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SENSATION

I. DEPTH, DISTRIBUTION AND PROBABLE IDENTIFICATION IN THE PREPUCE OF SENSORY END-ORGANS CONCERNED IN SENSATIONS OF TEMPERATURE AND TOUCH; THERMOMETRIC CONDUCTIVITY *

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In a recent paper (Bazett, McGlone and Brocklehurst [1]), data were reported of the temperature changes that accompany temperature sensations, and it was pointed out that inferences as to the mode of stimulation were unwarranted until the end-organs were more surely identified and their depth established. In that work the skin of the forearm was employed; in the present work the prepuce has been selected, since histologic study of fresh tissue removed at circumcision is possible. The prepuce has the additional advantage that a fold of two layers of skin may be obtained, which is less than 2 mm. thick. Consequently, the rate of penetration of heat may be measured and yet the abnormalities introduced by buried thermocouples be avoided. It is proposed in this paper to present physiologic evidence with a brief account of anatomic data. A more detailed account of the anatomic structures demonstrable in the prepuce will be presented in a later paper.

HISTOLOGIC STUDY

METHODS

The common means of identifying nerve terminations by means of silver or gold impregnations does not permit one to make determinations of their depth

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* This is the first of a series of three papers on sensation which will be published in this journal.

* The histologic work has been done entirely by R. G. Williams; H. M. Lufkin is responsible for the mathematical analysis to be found on pages 499 to 501; the other two authors are responsible for the physiologic work and for the arguments advanced.

1. Bazett, H. C.; McGlone, B., and Brocklehurst, R. J.: J. Physiol. **69**:88, 1930.

and distribution with relation to the surface without recourse to the laborious and frequently unsatisfactory method of sectioning and reconstruction. Nerve terminations have been successfully demonstrated in deeper tissues by Woollard (1926), who employed arterial injection of methylene blue (methylthionine chloride, U. S. P.) and cleared the specimens in oil of wintergreen. In a personal communication to us he described adaptation of this method to skin. It was tried on the human prepuce and found to be excellently suited for the purpose. The preparations were mounted in oil of wintergreen and remained unaltered for many months.

The skin to be examined was obtained within fifteen minutes after removal and pinned down to cork sheets so that the folds of the skin appeared as in life. An injection of a 0.05 per cent solution of methylene blue in Ringer's solution was made through the dorsal artery. All subcutaneous tissue was removed and the stain allowed to diffuse and develop. The extent of the staining was determined by frequent microscopic examination. When any visible nerves appeared intensely blue, the specimen was fixed on the cork in a 5 per cent solution of ammonium molybdate with 10 drops of hydrochloric acid for each 100 cc. of fixative, the fluid being kept below 4 C. The period of fixation usually required was about twenty-four hours. Subsequent treatment consisted of washing in water to remove the fixative, rapid dehydration in high alcohols and clearing in benzene, followed by oil of wintergreen. Such specimens were mounted between large coverslips, a number 1 and a number 3, thereby permitting observations from either side. The nerve endings were studied with a 4 mm. lens and their depth determined with the scale on the fine adjustment of the microscope. Surface position was determined by transposing the readings of the mechanical stage to a chart.

OBSERVATIONS

When so prepared and studied, the nerve endings in 1 sq. cm. of the human prepuce proved to be of seven morphologic types. Type 1 was a single fiber without an organized ending; type 2 was a small, nonencapsulated bulb made up of very fine, richly anastomosing branches; type 3 was made up of many branches, each ending in a number of smaller branches with small platelike terminations; type 4 was the encapsulated ending commonly called that of Krause; type 5 was a large, encapsulated ending having a nerve core surrounded by a lightly staining finely granular mass; type 6 was the large ending commonly called Ruffini's ending, and type 7 was the corpuscle of Meissner. The histologic structure of these endings is shown in figure 1. The capsules, when present, are not shown in the drawings; neither are the tactile cells of the Meissner corpuscle.[1a] The drawings are camera lucida tracings and show only the stained elements. The number and depth of each type of endings occurring in 1 sq. cm. is shown in table 1. The depths given are those observed for the most superficial part of the end-organ, and have been corrected for an observed shrinkage of 30 per

1a. In the original preparation typical tactile cells with a spiral arrangement identify type 7 as a Meissner corpuscle.

Fig. 1.—Camera lucida sketches of types of end-organs described in text. Types 1, 2, 3, 4 and 6 magnified 43.3 ×; types 5 and 7 magnified 200 ×.

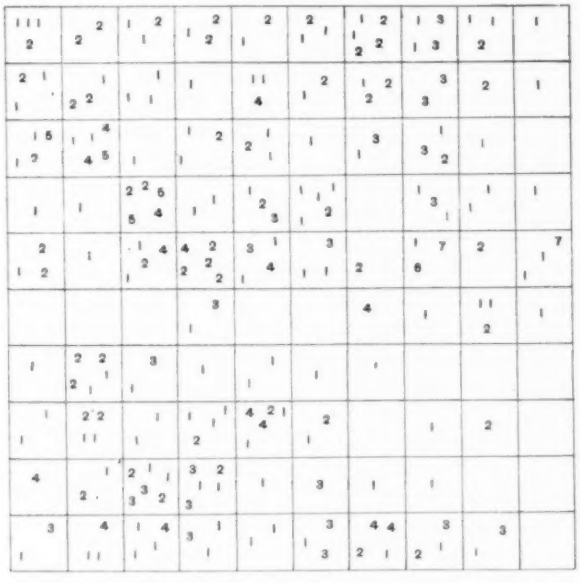

Fig. 2.—Spatial distribution in 1 sq. cm. of the seven types of end-organ described in text. The small squares represent 1 sq. mm. in extent.

cent during preparation. The spatial distribution of the endings in the same square centimeter of skin is shown in figure 2.

In the specimen from which this study was made the subcutaneous tissue had been cut away. Examinations of other specimens with this tissue largely intact indicate that many of the Ruffini endings lie in this deeper layer. They do not, however, appear to be more numerous than 2 or 3 to 1 sq. cm. of skin.

Spalteholz' diagram of the blood vessels in the skin has been shown to hold for the blood vessels of the prepuce. When the depth of the endings is compared with the depth of the blood vessel plexuses, types 1, 2, 3 and 4 are found in or peripheral to the arteriovenous region immediately below the corpus papillare of the corium; type 7, or Meissner's endings, lie in the region occupied by the second rete venosum

TABLE 1.—*Distribution and Depth of Seven Types of End-Organs in 1 Sq. Cm. of Skin of Prepuce*

Type	Number	Depth, Microns
1	115	80 – 103
2	52	28.6 – 40
3	23	57.1 – 85.5
4 (Krause)	15	91.4 – 103
5	4	131 – 200
6 (Ruffini)	1	285.7
7 (Meissner)	2	200

and type 6, or Ruffini's ending, probably deeper than this second rete venosum of Spalteholz.

Rudimentary hair follicles have been seen in some areas of the prepuce. They have no special nerve arrangement around them and many of them have none at all. They are few in number and widely distributed.

In order to determine which of the endings mentioned, if any, were in the epidermis, sections of the specimen were made in order to determine the thickness of the epidermis. The thickness of the epidermis was measured with an ocular micrometer and proved to be, at its maximum, 28 microns. Since the most superficial of the endings studied (type 2) occurred at a depth of approximately 28 microns, it is possible that some representatives of this type are in the deepest part of the epidermis, but most of the fifty-two counted occurred at a depth greater than 28 microns. It can be safely said, with the possible exception of a few of the type 2, that all of the endings seen were below the epidermis. Since intra-epithelial endings, when present, generally demand special treatment with gold or silver in order to be seen, it is not surprising that they were not demonstrated.

PHYSIOLOGIC STUDIES

TOUCH

Methods.—Two subjects only were employed; in subject 1 the ventral skin of the prepuce was used; in subject 2, owing to circumcision, the loose skin on the dorsum of the penis, 1 to 2 cm. proximal to the corona, was employed. A transverse fold was stretched and transfixed with small barbless fish-hooks at two points on the margin, from 2 to 3 cm. distant from one another. Each hook was attached to a 30 Gm. weight by a thread passing over a pulley, and the fold was in this way stretched and suspended in a vertical plane. If the hooks were inserted very close to the margin, the fold was very thin (from 1 to 1.5 mm.). An area of 1 sq. cm. was selected for investigation and by the use of a rubber stamp was ruled and divided into areas of 1 sq. mm. each. In neither subject have hairs been detectable on microscopic examination of the areas investigated. The threshold stimulus to touch was determined by a sudden impact of a light hair of adjustable length. The diameter of the hair was measured, and the pressure for varying lengths determined on a balance. The presence or absence of touch spots in any square was then determined by the use of a stimulus slightly above the threshold value. The whole fold was slung from a distance of from 10 to 15 cm. and could move freely when pressure was applied, and it is unlikely that the small stimulus deformed appreciably the more distant surface.

The reaction time to touch stimuli was determined by applying to the surface a very light copper wire (flattened ribbon of a galvanometer suspension) which formed part of a galvanometer circuit when a metal temperator, with a truncated conical end of 5 mm. diameter, was brought in contact with the skin. The temperator was maintained at a neutral temperature. The making of contact was recorded photographically by the deflection of a d'Arsonval galvanometer and sensation was signaled by air transmission to a tambour-mirror system. Contact was made by moving the temperator with a rack and pinion (Greenough dissecting microscope stand X. B. Zeiss), and was made as suddenly as possible. Corrections for errors due to parallax and air transmission were made.

Threshold.—The threshold for stimulation in this area was between 1.5 and 2 Gm. per millimeter radius of the hair (a pressure of from 90 to 120 mg. exerted on a hair, 0.12 mm. diameter).

Distribution of Touch Spots.—In subject 1, tested with a stimulus of 2 Gm. per millimeter radius, fifty-seven, sixty-two and sixty-eight of the hundred smaller squares ruled gave consistently negative responses in three areas of 1 sq. cm.; in subject 2, negative responses were obtained in sixty-seven, forty-six, seventy-one and sixty-nine under the same circumstances. When the stimulus was raised to 3 Gm. per millimeter radius, the number of areas giving negative responses in the last of these was only reduced to sixty-six. The data on subject 1 have a mean value of 62 and those on subject 2 one of 63. Since there is no surety that several touch spots may not be present in any given 1 sq. mm. in which positive responses were obtained, it has seemed wiser to tabulate on the basis of areas in which responses could not be elicited.

Several of the experiments were carried out with the assistance of Dr. H. Strughold of Würzburg. He also gave instructions in the technic and precautionary measures evolved by Professor von Frey.

Reaction Time to Touch.—Considerable variations were seen in the time of response, even though contact appeared to be made suddenly. The average time of response in subject 1 was 0.25 second (median 0.25, minimum 0.14, maximum 0.50 second); in subject 2, 0.32 second (median 0.29, minimum 0.14, maximum 0.57 second). A third subject was investigated and gave a mean value of 0.31 second (median 0.31, minimum 0.11, maximum 0.60 second).

COLD

Methods.—The prepuce was suspended as in the experiments on touch; a thermo-esthesiometer (Thunberg type), through which water circulated, with an apex of 1.5 mm. diameter, was used to map the presence or absence of cold spots. The fold of exposed skin, owing to its relatively great surface, assumed within a short time a temperature only 1 or 2 C. above that of the air; consequently, temperatures at about 15 C. were used in determining the presence of cold spots. In a few experiments designed for more accurate mapping, the spots were detected by copper wires (0.3 mm. in diameter, and from 2 to 3 cm. in length) soldered to heavy metal handles; these were cooled in ether within an ice-bath; on removal they dried rapidly but maintained for some time a sufficiently low temperature for stimulation in spite of the low temperature of the skin. Metal points at room temperature were ineffective.

The reaction times to cold stimuli were recorded in a manner similar to that used for touch; the time of contact of the temperator was determined from records of surface thermocouples at the point stimulated. In all the later experiments, a "point" consisting of a truncated cone with a surface of 20 sq. mm. (diameter 5 mm.) was used for stimulation. The prepuce as suspended showed a considerable movement with varying position of the subject and with his respiration; in addition, extensive contractions of the smooth muscle of the skin were often induced by stimuli or occurred rhythmically. It was therefore essential to employ a large applicator to ensure that the cold spot and thermocouple were adequately covered. The thermocouples employed have been McGlone loops of the lightest type previously described (Bazett, McGlone and Brocklehurst [1]), placed in similar positions on each surface, occasionally immediately superficial to the marked spot or more commonly about 1 mm. above or below the spot. They were secured by narrow strips of adhesive tape situated from 3 to 5 mm. from the thermojunction. Thermocouples buried within the tissues have only been employed in two control experiments designed to test thermal transmission.

The temperature changes were estimated from photographic records of the deflections of d'Arsonval galvanometers, as described in the reference cited. In the earlier experiments the periods of the instruments were the same as those described in that paper; in the later, and those from which the main deductions are drawn, the rapidity of the recording system has been improved without too great a sacrifice of sensitivity by employing a heavier galvanometer suspension, and by reducing the total resistance of the thermocouple circuit. The latter has been achieved by using thermocouples of about 14 cm. length, with the "constant" junction in a thermos flask (25 cc. capacity) containing paraffin oil

at room temperature. Thus, sudden changes could be recorded with an accuracy of about 0.02 C., but owing to alterations in the temperature within the thermos flask, the temperature levels could only be determined with an accuracy of 0.1 C. The periods of the galvanometers in these later experiments were such that, with the damping employed, when subjected to a constant electromotive force, the deflections reached the point of final equilibrium in 1 second, overswung 3 per cent beyond this value and returned to it in 2.3 seconds.

X-ray photographs were used to determine the thickness of the fold. The two surfaces were distinguished by the shadows of blobs of barium sulphate-glue paste placed on each surface (fig. 3). The thickness of the tissue was probably little influenced by compression during stimulation, since the fold was free to move; during application it was commonly moved through a distance of several millimeters.

Threshold.—No direct attempt has been made to determine the threshold stimulus. The temperature of the surface varied with the temperature of the room and the vascular condition of the fold, and the results obtained with varying stimuli will be considered in a later paper on the mode of stimulation.

Fig. 3.—Roentgenogram of a fold of the dorsal skin of the penis; transverse view. The thickness (1.2 mm.) is indicated by the distance between the shadows of the blobs of barium sulphate-glue.

Distribution of Cold Spots.—When an area of 1 sq. cm. of the skin was stamped and a small conical point or the fine wire described was used for identifying the spot, about from 10 to 20 per cent of the total number of squares usually gave positive responses, but in many squares the sensation produced would be one "slightly cool," in others "definitely cold." The former type of response was commonly obtained in squares adjacent to those giving the more definite sensation, and the effect produced was perhaps to be attributed to physical conduction of temperature changes. This seems probable, since these partial responses were more common on the distal margins of the more definite spots, where the term distal is applied according to the apparent direction of the blood stream. The number of sensitive spots within 1 sq. cm. which gave responses not attributable to a neighboring spot were from eight to twelve with the smallest stimulating surface.

With a point of 1.5 mm. diameter, and less exact differentiation, the sensitive areas appears to be slightly fewer, and the averages of

determinations by both methods give values of 7 per square centimeter for the prepuce of subject 1 (median 7.5, minimum 3, maximum 10); the areas investigated totaled 14.3 sq. cm. The average value for the dorsal skin of subject 2 was 6 (median 7, minimum 0, maximum 12); the areas investigated totaled 29.4 sq. cm. There was probably some overlapping of the areas investigated. In subject 2, a large area of about 17 sq. cm. was mapped, without being suspended; the number of spots detectable with a 1.5 mm. applicator was forty-three (2.5 per sq. cm.), though in many places from five to eight spots per square centimeter were identified. A considerable area of more than 1 sq. cm. was entirely deficient in cold spots; advantage was taken in this later in obtaining folds with cold spots limited to one surface.

Reaction Time to Cold.—Since it has been demonstrated that the reaction time to cold varies with the environmental conditions and other factors that modify the vascular conditions (Bazett, McGlone and Brocklehurst [1]), these factors must be briefly considered. In these experiments the room conditions should be classified as warm as far as the subject as a whole was concerned (effective temperature always above 17 C.), but for the exposed tissue it was cold. The blood supply of the prepuce was somewhat interfered with by stretching in an abnormal position, and the surface temperatures were usually low (mean 27.8, median 27.9, minimum 22.5, maximum 32 C.) The effect of inflammatory reactions from the supporting hooks can usually be neglected, since these were at a considerable distance.

When the thermocouples were placed directly over the cold spot, very long reaction times were commonly recorded, and the sensation of cold was also often very slight. With the thermocouples displaced to one side of the cold spot, these long reaction times were uncommon.

When a fold of skin was obtained, such that cold spots were present on one side and absent on the other, it could readily be demonstrated that the reverse stimulation of the cold spots from the opposite surface was possible, and that the reaction time under these circumstances was very long; the signal indicating sensation was then obviously more related to the temperatures on the further than to those on the nearer or stimulated surface. Even in areas where the cold spots were less irregularly distributed on the two surfaces, reverse stimulation from the opposite surface could be demonstrated, with applicators of both 1.5 and 5 mm. diameter, but it was more difficult to exclude the possibility of spread to a cold spot on the same side.

Comparison of the reaction times with stimuli applied to either surface with the rates of thermal transmission, calculable from the time relations of the temperature changes on the two surfaces, allowed approximate estimates to be made of the depth of the end-organs con-

cerned. Consequently the reaction times will be considered in relation to these calculations of the depths of the end-organs, and in a second paper in relation to their mode of stimulation.

Thermometric Conductivity.—The transmission of thermal changes, thermometric conductivity or diffusivity of heat must depend on the relationship of heat conductivity to heat capacity and specific gravity; if the thermometric conductivity be represented by the value a, then $a = \frac{b}{Kd}$ where b is the coefficient of thermal conductivity, K the heat capacity and d the specific gravity. In the tissues the values of both b and K may be considerably modified by variations in the amount and direction of circulating blood, so that the system appears too complicated to be considered on such fundamental principles.

The thermocouples record not average surface temperature but that of small grooves in the skin into which they are pressed and where their temperatures may be much modified by the proximity of large vessels. Consequently, in some cases

TABLE 2.—*Transmission Rate of Cold and Warmth (Millimeters per Second)*

	Subject 1. Prepuce		Subject 2. Dorsal Skin of Penis	
	Inside to Outside	Outside to Inside	Proximal to Distal	Distal to Proximal
Cold				
Mean	0.85	0.86	1.15	0.87
Median	0.86	0.78	1.21	0.88
Minimum	0.57	0.69	0.77	0.36
Maximum	1.20	1.32	1.47	1.37
Warmth				
Mean	1.04	0.91	1.10	0.85
Median	1.03	0.87	0.93	0.82
Minimum	0.67	0.69	0.62	0.40
Maximum	1.57	1.34	1.74	1.26

the thermocouple on the surface touched may record even smaller changes than that on the further surface (see succeeding paper). The rate of thermal transmission is also much affected by the vascular distribution. In the dorsal skin of subject 2 where the vascular distribution is relatively regular, the elapsed time to the first detectable thermal change on the far surface was always less from the proximal to the distal surface of the transverse fold than vice versa; in one case the former was only 47 per cent of the latter. In the prepuce of subject 1, similar differences were observed, with a maximum difference of from 67 to 100, but they were irregular in direction. Presumably these differences depended on the relationship of the direction of thermal conduction to the main paths of arteries and veins, and also to the degree of spread of heat laterally into other areas. The range of values for apparent transmission rate in the two subjects is given in table 2; they are for the most part somewhat more rapid than those observed for similar distances in the forearm (Bazett, McGlone and Brocklehurst [1]), even in those experiments where the galvanometer systems employed were identical. Vasoconstriction from exposure may have been concerned, for the rates were most rapid on the colder days.

In three experiments on subject 2, stasis was produced by clamping a part of the fold with a light clamp of the intestinal type. Under these conditions there was a slowing of the original transmission rate (about 30 per cent) to one of about 1 mm. per second, and the conduction rate in the two directions was then

approximately the same. On removal of the clamp there was a marked and persistent hyperemia, partly due to inflammation, since the clamp produced some injury and was painful. During such hyperemia, the differences in transmission rate in the two directions became much in evidence, though the actual rate might be either greater or less than that observed during stasis, and commonly varied from stimulus to stimulus. The highest rate ever observed (1.9 mm. per second) was, however, seen in a proximal-distal direction under these circumstances.

When the tissue and its circulation was relatively uniform, the curves obtained might be relatively regular. An example is reproduced in figure 4. This particular record was employed to determine the error introduced by galvanometer lag; the curves were read under a microscope in a comparator and were then analyzed by the method devised by Hill and Hartree;[2] the curves recorded on closure of

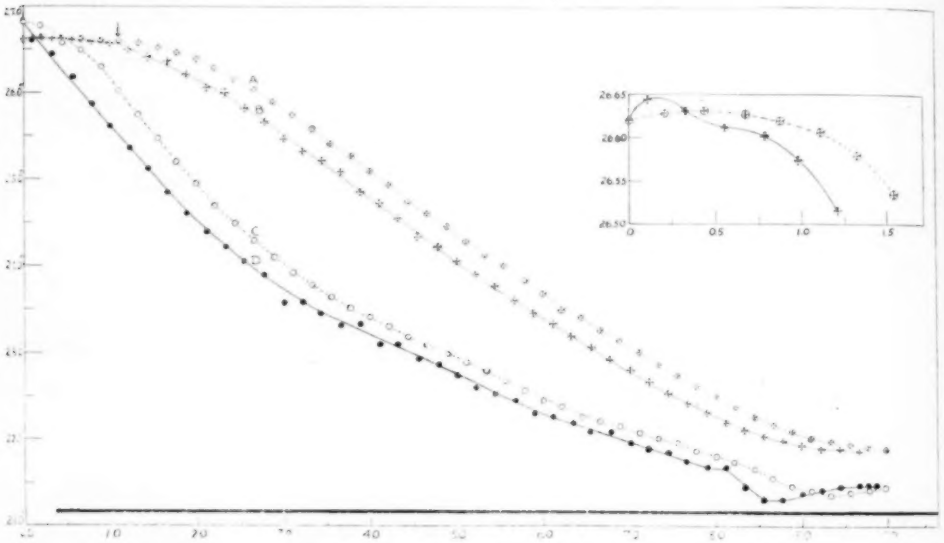

Fig. 4.—Recorded and analyzed curves of change in temperature of near, or stimulated, and far surface of a fold of the dorsal skin of the penis 1.4 mm. thick. The recorded curves are: *A*, far surface; *C*, near (anatomically distal) surface. The analyzed curves are: *B*, far surface; *D*, near surface. The cold spot was near the distal surface. A temperator of 5 mm. diameter was applied at 15.6 degrees (stimulus, 11.22 degrees) for 9.25 seconds. Sensation, recorded latency 0.34 second (presumably induced 0.14 second earlier) continued 1.47 seconds after removal of the stimulus, was reported as "sharp cold." The room was "warm," i. e. > 17 degrees effective temperature. The ordinates represent the temperature of the surface (Centigrade); the abscissas, the time in seconds. The apparent exaggeration of the temperature change commencing on the near surface at 8.1 seconds was caused by the thermocouple springing back slightly and following the applicator during its removal.

On the inset are drawn the recorded and analyzed curves of far surface for a period of 1.55 seconds following stimulation. The ordinates and abscissas are as in the main chart (units greater).

2. Hill, A. V., and Hartree, W.: J. Physiol. **54**:84, 1920.

the circuit were used as control curves. The curves as actually recorded and as determined by analysis are both illustrated, and the start of the change on the more distant surface is shown on a larger scale in an inset. It will be noticed that the start of the change on this surface is somewhat complicated by an initial slight rise of temperature presumably dependent on some vascular change induced by pressure. The actual fall appears on analysis to have commenced after from 0.5 to 0.8 seconds, though when read with a hand lens the fall did not appear to start for 1.1 seconds. It is the latter method that has been employed in other records, and, though the earliest possible time for a detectable change of temperature has been used, it is probable that the real times are somewhat shorter; since

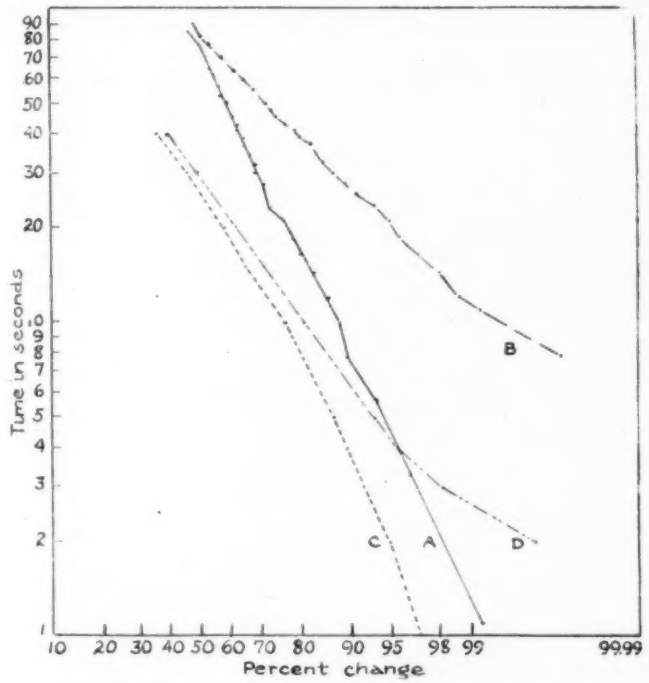

Fig. 5.—Data of figure 4 plotted on logarithmic probability paper. *A* indicates the near surface; *B*, the far surface; the rate of recovery is also shown; the near surface by *C* and the far surface by *D*. The equilibrium points assumed were: near surface, 16.6 degrees; far surface, 17.6 degrees. The time values of the stimulus curves in this case are one tenth of the value shown on the ordinate scale.

the temperature change starts asymptomatically, the actual start is not exactly determinable.

The curves recorded are of the skew probability type. With stimuli of long duration the final equilibrium point may be determined; with cold stimuli these are usually less than 1 degree above the applicator for the near surface and about 1 degree above it for the far surface; with warm stimuli, 1 degree below the applicator for the near and from 2 to 3 degrees below for the far surface. These approximate values may be used to estimate the probable equilibrium points for

parallel stimuli of shorter duration, and the percentage distance from these equilibrium points in both types of experiment may be plotted as a function of the time on logarithmic probability paper (Karsten [3]). The curves approximate straight lines. The analyzed curves of figure 4 are so plotted in figure 5, together with curves representing the recovery of the original temperature (in this case without correction for galvanometer lag). Times are measured for both surfaces from the moment of contact or removal of the applicator.

This method of plotting is equivalent to transforming the time to its logarithm and the percentage of change of temperature p toward an assumed equilibrium point with respect to time t to values of the normal probability integral, which may be obtained from a table of deviates of the normal curve. The mathematical expression becomes

$$(1) \qquad p = \frac{100}{\sqrt{2\pi}} \int_{-\infty}^{w} \epsilon^{-\frac{w^2}{2}} dw$$

where w is of the form

$$w = \frac{\log_\epsilon t - b}{m}$$

b and m being parameters that vary from experiment to experiment and also sometimes during the course of a single experiment. These parameters are determined from the empiric data by making the transformations as previously given and determining the best fitting straight line of the form $t = mp + b$, using the method of least squares. The parameter b is the natural logarithm of the time at which there has been a change of 50 per cent toward the assumed equilibrium point; the significance of the parameter m is unknown; it is, however, always negative.

If equation 1 is differentiated with respect to t

$$(2) \qquad dp/dt = \frac{100}{\sqrt{2\pi}} \frac{1}{mt} \epsilon^{-\frac{w^2}{2}}$$

Equation 2 gives the rate of change of p for any value of t; using it to determine maximum values of dp/dt, it is found that this occurs when

$$t = \epsilon^{b - m^2}$$

The values of $\frac{1}{\sqrt{2\pi}} \int_{-\infty}^{w} \epsilon^{-\frac{w^2}{2}} dw$ and of $\frac{1}{\sqrt{2\pi}} \epsilon^{-\frac{w^2}{2}}$

may both be read from table 2 of Pearson's tables (Pearson [4]) where the value of the integral for any value of w is given in the column $\frac{1}{2}(1 + \alpha)$ and the second value from the column headed Z.

Curves are plotted in figure 6 to represent the changes with a long cold stimulus and in figure 7 those with a short warm stimulus. There often appears to be a definite and sudden change of slope at some point; particularly is this true of the more distant (inside) surface in figure 7. The angular change in slope in figure 7 may depend on the removal of the stimulus since it occurs at

3. Karsten, K. G.: Charts and Graphs, New York, F. F. Prentis Hall, 1925.

4. Pearson, K.: Tables for Statisticians and Biometricians, London, Cambridge University Press, 1914.

about this time or it may represent some physiologic (presumably vasomotor) alteration in the tissue, for it appeared to be associated with a change in sensation. The actual record from which figure 7 is derived is shown in figure 8; a sudden increase in the sensation of warmth was recorded 4.3 seconds after contact, and the change in slope on the far surface occurred after about 5 seconds. Since the end-organ for warmth in this case probably was situated 0.3 mm. nearer the applicator than this surface, the two changes appear related. Vasomotor changes seem more likely to be the cause than mechanical effects of pressure in some cases, since changes in slope may be seen during recovery.

The values of the constants b and m for the curves of figure 7 are given in table 3, and from these, by the use of equation 2, the rates of change (dp/dt)

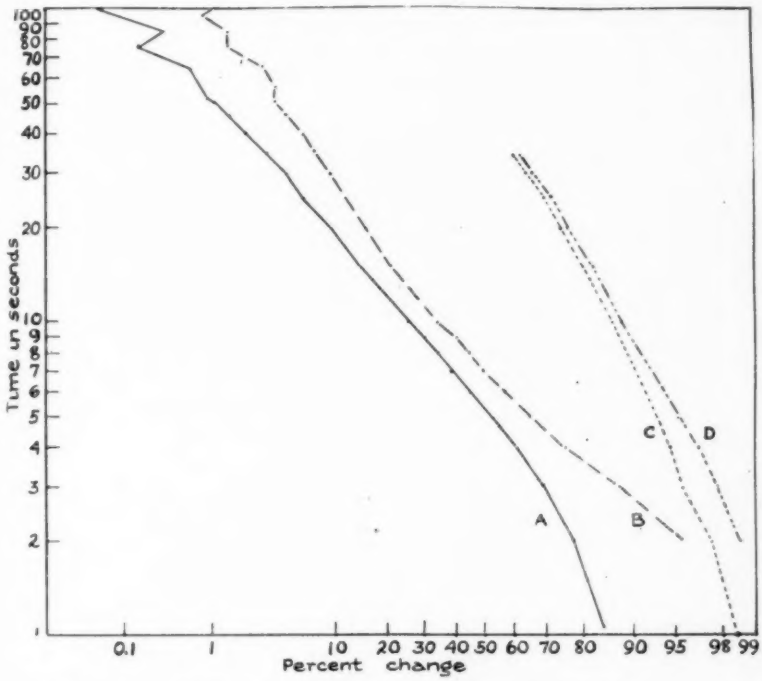

Fig. 6.—Stimulus of 17.1 C. (— 6.4 C.) for 3 minutes and recovery plotted as in figure 5. The stimulus was applied to the anatomically distal surface of the dorsal skin of the penis 1.15 mm. thick. The equilibrium points assumed were: near surface, 17.2 degrees; far surface, 17.65 degrees. The room temperature was 22.5 C. dry bulb (lowest employed with cold stimuli). The time values are computed according to the scale. The curves are as indicated in figure 5. Some data of this experiment are also shown in figure 5 of succeeding paper.

have been calculated; they are shown graphically in figures 9 and 10. The values of both parameters b and m must be influenced by many physiologic and physical factors, including thermal conductivity and capacity and the effects of the circulation on them, as well as by the depth. The small thickness of the prepuce makes this tissue unsuitable for investigating the exact relation of these parameters to depth, and further experiments on the forearm are being undertaken with the hope of elucidating this point.

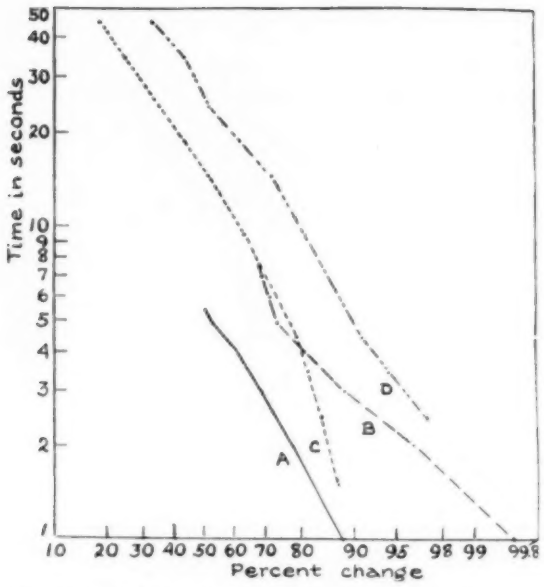

Fig. 7.—Stimulus of 41.1 C. (+ 13.2 C.) for 5.5 seconds and recovery plotted as in figure 5. The stimulus was applied to the outer surface of the prepuce fold 1 mm. thick. The equilibrium points assumed (on basis of long stimulus in the same series) were: near surface, 40.4 degrees; far surface, 37.9 degrees. The time values are computed according to the scale. The curves are plotted as indicated in figure 5.

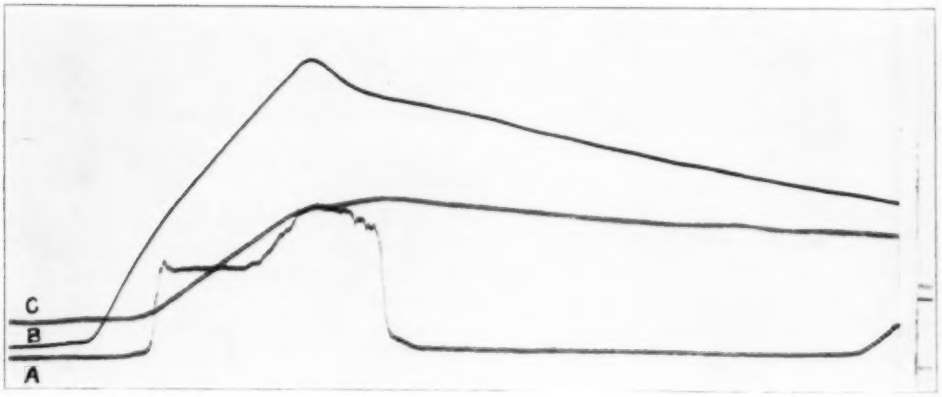

Fig. 8.—Part of the actual record subjected to analysis in figure 7. *A* indicates the subjective record of sensation of warmth increasing in intensity where the upstroke is exaggerated; *B*, the temperature changes on the near (outer) surface; *C*, the temperature changes on far surface (fold 1 mm. thick). The temperature factor in *B* was 0.955 C.; in *C*, 1.112 C. per centimeter. The speed was 9 mm. per second. The initial temperature in *B* was 27.95 C.; in *C*, 27.95 C. The maximum temperature in *B* was 34.1 C.; in *C*, 31.05 C. One interval of 30 seconds is omitted. Figure reduced 0.6 ×.

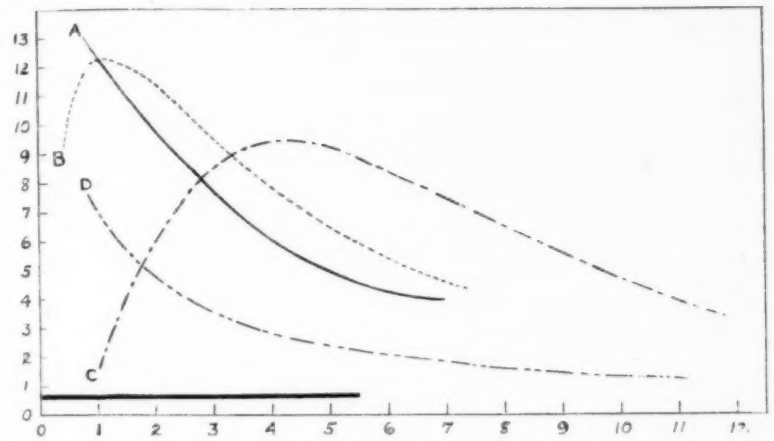

Fig. 9.—The rate of change (dp/dt) calculated according to equation 2 for the stimulus illustrated in figures 7 and 8. The calculations were made from the constants given in table 3. *A* indicates the rate of change on the near surface under conditions at the start of the stimulus (constant a); *B*, the rate of change during the later part of the stimulus; *C*, the rate of change on the far surface at the start of the change; *D*, the rate of change during the later parts of the stimulus. The duration of the stimulus is shown by a solid line near the abscissa. Times are plotted from the moment of contact. The ordinates represent the rate of change; the abscissas, time in seconds.

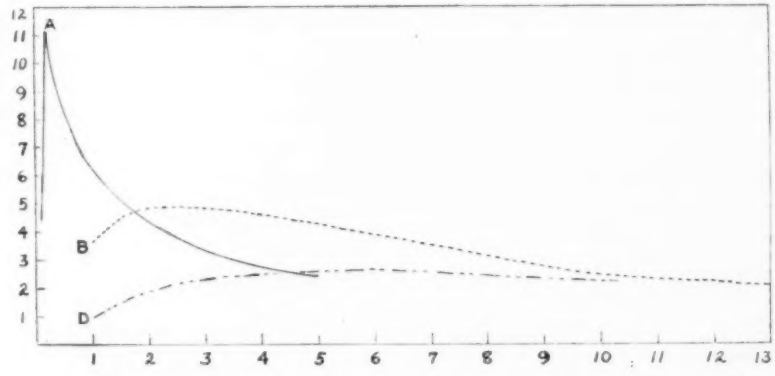

Fig. 10.—The rate of change (dp/dt) in recovery calculated as for figure 9. The curves *A*, *B* and *D* are the same as in figure 9. Times are plotted from the moment of removal of the applicator. The ordinates and abscissas are the same as in figure 9.

However, it is possible to achieve approximate estimates. In two experiments a third thermocouple was buried in the prepuce between the two surface thermocouples, and it was found possible to estimate the depth of this couple by assuming a simple linear relationship of the start of the change to depth. Thus, in one experiment a double fold of prepuce had a thickness of 1.75 mm. and the buried couple was 0.8 mm. from the outside as shown by roentgen examination.

The rates of transmission were very different, 1.1 mm. per second from inside to outside and 0.6 mm. per second in the reverse direction. Application was somewhat slow and the curves were consequently complicated by radiation effects. Even so, the estimates on a linear hypothesis of transmission rate were 1.08 mm. from the outside when the applicator was applied to this side, and 0.49 mm. with stimulation of the other side. The mean estimate at depth was therefore correct (0.78 mm.), since the two errors tended to neutralize one another. The maximum rates of change were estimated for all three couples by drawing tangents to the curves. These appeared to be related according to the following equation

$$\log r_d = \log r_1 - \log d \left(\frac{\log r_1 - \log r_2}{\log D_2 - \log D_1} \right)$$

TABLE 3.—*Values of Parameters m and b for the Experiment Shown in Figure 7*

	m	b
Outside (near) (a)	1.583	1.878
Outside (b)	1.237	1.722
Outside recovery (a)	2.534	3.416
Outside recovery (b)	1.303	2.688
Inside (far) (a)	0.752	2.007
Inside (b)	2.702	3.291
Inside recovery	1.263	3.293

where r_d is the maximum rate of change in degree Centigrade per second at depth d, r_1 and r_2 the maximum rates of changes on the two surfaces at depths D_1 and D_2. Since the thermocouple on the near surface was embedded in a groove during stimulation, its effective depth was considered as 0.02 mm. The change at depth d at some time t after contact may be considered as that induced in $t - \frac{d}{v}$ seconds after the start of the change at this depth, where v is the apparent velocity of thermal transmission estimated from the changes on the two surfaces. If $\Delta \theta_1$ and $\Delta \theta_2$ represent the changes in $t - \frac{d}{v}$ seconds on the two surfaces, then the following equation is found to hold

$$\log \Delta \theta_d = \log \Delta \theta_1 - \log d \left(\frac{\log \Delta \theta_1 - \log \Delta \theta_2}{\log D_2 - \log D_1} \right)$$

Though these equations are empiric, and can probably only be used over a narrow range of values, yet within limits a fair approximation may be expected, as may be seen in table 4. Consequently, in dealing with the data for the present these equations have been used, employing slide rule and logarithmic graph paper for the estimations.

Calculation of the Depth of the End-Organ for Cold.—It has already been pointed out (Bazett, McGlone and Brocklehurst [1]) that the reaction time may be considered as involving three factors, the minimum

time (n) for the nervous process of reaction, the time taken for the temperature changes to reach the end-organ $\frac{d}{v}$, where d is the depth of the end-organ, and v the average rate of transmission of thermal changes to this depth, and the time (x) necessary for the thermal changes to reach a threshold value. This last value x would include the time consumed in overcoming a block in the synapses of the nervous system, since this time presumably varies with the strength of the stimulus and the frequency of impulses ascending the sensory nerve (Adrian and Zotterman,[5] Bronk[6]). The reaction times from the two surfaces (t_s and t_{sr}) might then be represented by the following two equations:

$$t_s = n + \frac{d}{v} + x$$

$$t_{sr} = n + \frac{D - d}{v} + x$$

where D indicates the total thickness of the fold, and all values are expressed in millimeters and seconds.

TABLE 4.—*Comparison of Calculated and Observed Changes at a Depth of 0.8 Mm.*

Stimulus	Maximum Rate of Change on Outside, °C. per Sec.	Maximum Rate of Change on Inside, °C. per Sec.	Maximum Rate of Change at 0.8 Mm. From Outside, °C.		Total Change on Outside, °C. in 2.8 Sec.	Total Change on Inside, °C. in 2.8 Sec.	Total Change at 0.8 Mm. From Outside in 2.8 Sec.	
			Estimated	Observed			Estimated	Observed
Outside								
17.0° (—10.8°)	3.20	0.150	0.60	0.52	2.08	0.20	0.30	0.39
41.4° (+12.3°)	1.70	0.325	0.43	0.42	3.33	0.42	0.59	0.55
Inside								
16.7° (—11.0°)	0.085	1.07	0.12	0.115	0.13	1.76	0.18	0.18
43.0° (+14.2°)	0.205	4.30	0.31	0.32	0.22	3.60	0.32	0.34

A first approximation of the depth of the end-organ may be obtained by the assumption that in direct stimulation from the nearer surface the sum of the values n and x may be similar in magnitude to the sum of these values in the sensation of touch. The differences in latency of the two sensations would then be attributed almost entirely to differences in transmission times (assuming that of touch to be negligible), and the equation can be represented by

$$t_s = n^1 + \frac{d}{v}$$

Calculations have been made in this way, assuming the value of n^1 to be 0.14 second, when dealing with minimal reaction times to cold, and giving n^1 the respective values observed for touch in the subject concerned when dealing with either mean or median values of the reaction times. As far as the calculations from minimal reaction times are concerned, the values obtained are likely to be greater than the true depth,

5. Adrian, E. D., and Zotterman, Y.: J. Physiol. **61**:151 and 465, 1926.

6. Bronk, D. W.: J. Physiol. **67**:270, 1929.

since a value for n^1, of 0.14, which assumes a zero value for x, is likely to be an underestimate. The estimates of depth d from minimum reaction times gave the following values: mean, 0.19; median, 0.19; minimum, 0.11, and maximum, 0.30 mm. The distribution of the estimates from mean, median and minimum values is shown in figure 11. These estimates are distributed on either side of the median value (0.17 mm.) in a normal probability curve. The agreement with calculations from the minimal reaction times, where systematic errors probably exaggerate the depth, suggests that systematic errors of this type are present and that the real depth is likely to be less than this. One of about 0.1 mm. is assumed.

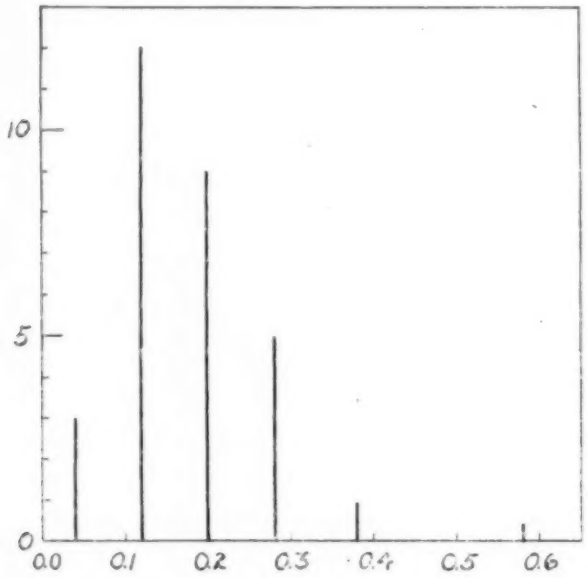

Fig. 11.—Distribution of mean, median and minimum values for d for cold end-organ, as calculated on the "n" basis, in classes of 0.1 mm. (— 0.05 to 0.04, etc.).

Comparison may then be made of stimuli which produced similar rates of change at this depth regardless of the side stimulated, and the depth may then be recalculated on the assumption that x (and therefore $n + x$) is constant under such circumstances. If $n + x$ be represented by y, the equations already given can be solved, and occasionally such solutions appear valid. For instance, in one of the earlier experiments when an applicator with a surface of 1.5 mm. diameter was employed, and the thermocouple lay directly over the sensitive spot, very long reaction times were obtained from both surfaces. Nevertheless, when two stimuli are compared, in which the maximum rates of change at

0.1 mm. depth from the more sensitive surface were probably 0.75 C. and 0.55 C. per second, the following equations are obtained:

$$\text{Direct stimulation } 1.82'' = \frac{d}{1.455} + y$$

$$\text{Reverse stimulation } 2.83'' = \frac{1.5 - d}{1.21} + y$$

and values of 0.15 mm. for d and 1.72 seconds for y are calculated. Similarly, the data of another experiment indicate a value for d of 0.11 mm. and a value for y of 0.18 second; in this experiment, reverse stimulation gave a maximum rate of change almost twice as great as that observed with direct stimulation (1.33 C. per second as compared with 0.70 C.) and the reaction times were short (0.97 second reverse and 0.21 second direct).

However, in most cases the assumption of a constant value for y regardless of the side stimulated appears unwarranted, for negative values for d or y may be obtained.

Negative values for y are found whenever difficulty has occurred in finding an area with cold spots on only one surface, and the results probably depend on stimulation of end-organs belonging to both surfaces. Negative values for d have been obtained in cases in which the existence of end-organs on only one surface has been certain, and presumably depend on some factor involved in stimulation. Two examples are given.

In subject 1, two direct stimulations gave rates of changes at 0.1 mm. of about 1 and 1.13 C. per second, and two reverse stimulations produced at the same depth changes of 1.02 and 1.03 C. per second. The reaction times to the former were 0.39 second and 0.39 second, and to the latter 1.35 second and 1.81 second. Calculations give a depth of — 0.34 mm. for the end-organ. If, however, the time of thermal transmission be calculated on the basis of the interval to the maximum rate of change (rather than to the apparent start of the change), the value for d becomes 0.17 mm. and that for y 0.09 second. Data of this experiment may be found in table 1, experiment 2 of the following paper.[7] Even such modifications of the mode of calculation may not be warranted, for in another experiment on subject 2, two successive stimuli on opposite sides gave identical estimates for maximum rate of change at 0.1 mm. below the more sensitive surface, but absurd values for d are obtained, even when thermal transmission is estimated on the basis of the time to the maximum rate of change. When estimated on this basis, the value for d obtained is — 0.7 mm; when the velocity is estimated on the basis of the start of the temperature changes d has a value of — 2 mm.

Since so many anomalous results may be obtained by the second method of calculation, it would appear that the assumption of a constant value for y is only occasionally warranted, and that calculations of this

7. Bazett, H. C., and McGlone, B.: Studies in Sensation: II. The Mode of Stimulation of Cutaneous Sensations of Cold and Warmth, Arch. Neurol. & Psychiat., to be published.

type are unreliable when dealing with data of cold stimulation, even though they appear to give valid results in the case of warmth, as will be seen later.

Consequently, only the first method can be employed, and this indicates a depth somewhat less than 0.17 mm., since systematic errors are apt to have exaggerated the depth, a real depth of about 0.1 + 0.05 mm. can probably be assumed.

WARM

Methods.—The methods adopted were the same as those used for cold, except that the distribution of the spots was determined entirely with a temperator with a point of 1.5 mm. diameter, maintained at about 40 C.

Threshold.—As in the case of cold, this will be discussed in a later paper.

Distribution of Warm Spots.—The warm spots have been somewhat unevenly distributed; they have been particularly in evidence in the neighborhood of large veins, and have often appeared to lie directly over these, or somewhat to one side over a small but visible branch. Not infrequently, diffuse sensations of warmth have been obtained when the temperator has been applied along the path of the vein distal to the most sensitive area.

On the colder days, when the temperature of the prepuce had fallen, the warm spots were less easily stimulated, when the tissue was stretched, provided that the veins were constricted and no longer clearly visible. The number demonstrable in subject 1 varied between 0.45 and 1.8 per square centimeter, with a mean value of 0.9 (area examined 11.7 sq. cm.); in subject 2, they varied between 0.6 and 1 with a mean value of about 0.7 (area examined 26.4 sq. cm.). In subject 2, the lowest value was obtained in the large area of 17 sq. cm. (mapped without suspension) in which only ten spots were identified; an area was included which was particularly free from temperature sensations. The warm spots may be considered as 1 per square centimeter or slightly greater if some spots failed to respond (compare Rein [8]).

Reaction Time to Warmth.—The rooms were warm, as in the experiments on cold sensations, except in two cases, where the room temperature (dry bulb) was about 20 C. and the effective temperature below 17 C. The initial surface temperatures were similar to those observed with cold, except on these two cold days when initial temperatures as low as 22.4 C. (subject 1) and 23.5 C. (subject 2) were recorded. Reaction times were longer than those observed with cold stimuli, and usually were definitely much shorter from one surface than from the other. The sensation with the shorter latency had a much more abrupt

8. Rein, H.: Ztschr. f. Biol. **82**:513, 1925.

and definite onset, and was often, but not always, more intense, and if the position of the fold was altered the end-organ appeared to move definitely with the more sensitive surface. Occasionally the reaction times from the two surfaces were similar in duration, and the intensities of the sensations were then sometimes also similar.

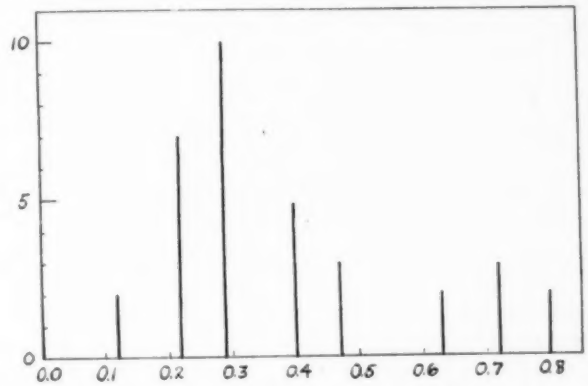

Fig. 12.—Distribution of mean, median and minimum values for d for warm end-organ, as calculated on the "n" basis, in classes of 0.1 mm. (0.05 to 0.14, etc.). The ordinates and abscissas are the same as in figure 10.

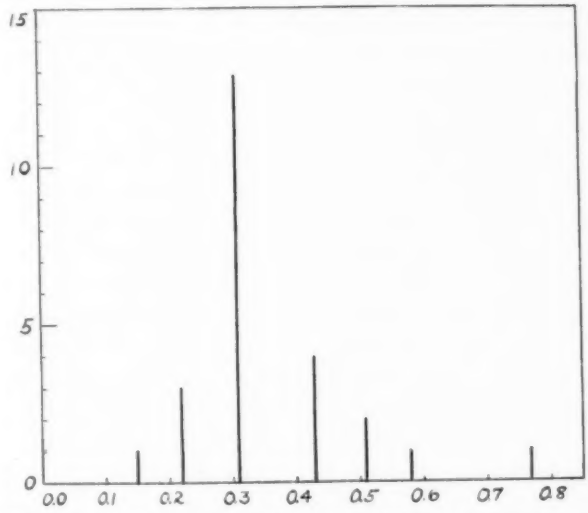

Fig. 13.—Distribution of mean, median and minimum values for d for warm end-organ, as calculated on the "y" basis, in classes of 0.1 mm. (0.05 to 0.14 etc.). The ordinates and abscissas are the same as in figure 10.

Calculation of the Depth of the End-Organ for Warmth.—Calculations may be made as in the case of cold. Estimates made by assuming values for n^1 similar to those for touch have a median value of 0.28 mm.

Calculations may also be made by the use of the second method, in which $n + x$ is assumed to be unaffected by the direction of stimulation. Values may be calculated in this way from the mean, median or minimal latencies on the two sides. In a few experiments where two or more individual stimulations appear particularly significant, calculations have also been made from data so selected. In this way, by the use of the two methods, six or seven estimates may often be made of the depth d in any single experiment, though in certain cases some of the results obtained by one or the other method must be discarded. The first method may occasionally give a depth from the nearer surface greater than half the total thickness of the fold, when the reaction times are unusually long. The second method may sometimes give negative values for $n + x$ (two experiments), and the depth calculated has then been near the center of the fold; in this case two separate end-organs may be concerned in the responses. The second method has also in two experiments given negative values for d; these may be due to an occasional inefficiency of reverse stimulation, similar to that commonly observed in the case of cold. When these anomalous results are discarded, the estimates made by the two methods are similar. The frequency distribution of estimates obtained by the first method is shown graphically in figure 12, by the second in figure 13. In both curves the values are distributed about a 0.28 to 0.32 mm. value according to probability curves, if the few values between 0.5 and 0.8 mm. are considered separately. In a total of thirteen experiments, both methods of calculation were applicable in eight, and in six of these the discrepancy between the results obtained by the two methods had a mean value of 0.07 mm. In the other two experiments the results were complicated by an experimental procedure designed to test the mode of stimulation rather than the depth. The values obtained for $n + x$ in the calculations are not unreasonable, considering the variations of the conditions and possible errors; the following values were calculated: mean, 0.41; median, 0.34; minimum, 0.06; maximum, 1.80 seconds.

One is therefore warranted in assuming an average depth of 0.3 ± 0.05 mm. for the end-organ for warmth. The occasional occurrence of estimates of from 0.5 to 0.7 mm. in the center of the fold between the two layers may indicate that the end-organ may sometimes occupy a subdermal position, for such estimates were obtained in two experiments with calculated values for $n + x$ of from 0.18 to 0.61 second. However, one cannot exclude the possibility that they may result (as those where $n + x$ has a negative value) from the presence of two separate end-organs.

Comparison with Histologic Data.—It will be seen in table 1 that over 200 end-organs may be demonstrated histologically in 1 sq. cm. of skin,

and that these belong to seven morphologic types. In addition, pacinian and Golgi-Mazzoni corpuscles may be occasionally demonstrated in the deeper layers of the dermis. Correlation of sensations of touch and temperature with some of these types may be attempted. There can be little doubt of the correctness of the orthodox view that the branching fibrils of group 1 subserve pain, and the distribution of the remaining types may therefore be compared with that of sensations of touch and temperature.

Touch.—The area of deformation in stimulation with a hair is hard to estimate. It is probably approximately 1 sq. mm., since squares giving positive responses usually do so repeatedly even though the exact point of application varies, and yet consistent negative responses may be given by a square surrounded on two or three sides by squares sensitive to touch. Since from 29 to 54 per cent of the squares give positive responses, touch sensations cannot be accounted for by types 5, 6 or 7. Types 3 and 4 are unlikely to be responsible. Type 3 is absent in about 83 per cent, type 4 in 86 per cent of the squares, and to explain touch sensations on the basis of these end-organs would only be possible if the area of deformation extended over a circle of some 2 mm. diameter. Negative squares surrounded by positive ones would then be difficult to account for. Type 2 is absent in 64 per cent of the squares (fig. 2) and touch sensations are not detectable usually in from 62 to 63 per cent of the squares. While it is probable that a single sensitive end-organ of this type near the margin of a square would give positive responses in two squares, it is equally possible that negative responses may be recorded in a square even though an end-organ is really present near its margin. The distribution of type 2 would therefore correspond well with that of touch, if the area of deformation be supposed to extend over a circle of from 0.5 to 1 mm. diameter. Type 2 is probably associated with touch sensations in the prepuce. These end-organs are found at a depth of from 0.03 to 0.04 mm., just below the epidermis, which has a thickness in the prepuce of 0.01 to 0.03 mm.

Cold.—Of the types of end-organ described, only those of types 3 and 4 could be considered as having a distribution that could possibly be correlated with that of cold spots, and of these type 4 (Krause) has the better correlation. The number of Krause end-organs observed is greater than the number of cold spots commonly found physiologically, but, as in the case of touch, this is likely to be the case, for Krause end-organs often occur in groups of two or three and these can only be recognized physiologically as a single unit. Sommer (cited by von Frey[9]) has described as many as twenty-three cold spots in a single square centimeter on the prepuce (more than in any other area of the

9. Sommer, cited by von Frey, M.: Tabulae biol. Berlin **2**:268, 1925.

body); the possibility that during testing end-organs on the opposite side were stimulated cannot be excluded. There is therefore good agreement with the histologic data in spatial distribution, and the depth estimated physiologically also agrees with that of the Krause ending. It has to be admitted that the assumption that the synapse delay for temperature is the same as that for touch has no inherent probability; it might well be slightly longer, and consequently the depth calculated be too great. But in view of the comparison with histologic data, and of the agreement in the case of warmth between the two methods of calculation, the assumption is justifiable. There is therefore very good evidence confirming the observations of Strughold and Karbe[10] that Krause's end-bulbs are responsible for cold sensations. The observations of these workers (as well as earlier observations by von Frey) showed that the cold spots were close to blood vessels. Histologic data demonstrate that the Krause end-organs occur close to a capillary loop in a papilla (Ruffini[11]) or in the arteriovenous region immediately below the papilla, if the superficial end-organs of the Krause type here described be identified with the "monolobaire" corpuscles of Ruffini.

Warmth.—The only end-organs that could possibly be correlated with the spatial distribution of warm spots are those of types 5, 6 and 7. Of these, type 5 are much more numerous than would be expected and their depth of less than 0.2 mm. seems entirely out of agreement with the physiologic data; type 7 has the structure of a Meissner corpuscle, and there is no reason not to refer to it functions of touch. Those of type 6—Ruffini's corpuscles—have both a spatial distribution and a depth which correspond with those determined physiologically. On physiologic evidence the end-organs for warmth are sometimes subdermal; Ruffini stated that his end-organ occurs most commonly subdermally, and it has been found also in this position in the prepuce. On histologic evidence many of these end-organs appear to lie between the second and third venous plexuses of Spalteholz, possibly deep to the subpapillary arteriolar plexus. In the forearm, physiologic evidence suggested a depth superficial to this arteriolar plexus. Further work on this apparent discrepancy is being attempted.

COMMENT

Touch.—Meissner's corpuscles are only demonstrable in prepuce material at a considerable depth and only one or two are present per square centimeter. Since sensitivity to light touch is widely distributed, they cannot therefore in this area be responsible for such sensations, though they may well account for sensations produced by more extensive

10. Strughold and Karbe: Ztschr. f. Biol. **83**:189, 207 and 297, 1925.
11. Ruffini, G.: Rev. gén. d'histol. **1**:425, 1905.

deformation of the skin. As hairs are also absent, sensations of touch are presumably accounted for by the atypical nonencapsulated end-bulbs of type 2 here described. The evidence for the relationship of Meissner's corpuscles to touch in other hairless areas is good and has been recently reviewed by von Frey and Rein;[12] the data from the prepuce reported here should not be regarded as necessarily in conflict.

Cold.—The theory of the dependence of cold sensations on Krause's end-organs, suggested by von Frey[13] and confirmed for the conjunctiva by Strughold and Karbe[10] and by Strughold[14] on the basis of very careful experiments, has in spite of this remained open to criticism. Waterson[15] emphasized the variability of the number of cold spots, and even suggested that the law of specific nerve energies may be untrue, while Dallenbach[16] advanced similar revolutionary ideas. Such viewpoints are unwarranted. Waterson paid no attention to the vascular factors in sensation to which Ebbecke[17] drew attention, nor did he consider the great variations in thermal conductivity which must result from the vascular changes with which he experimented. Dallenbach has no evidence except the failure to demonstrate end-bulbs beneath cold spots, and the same is true of the work of Pendleton.[18] Their histologic methods may have been inadequate.

Pendleton introduced an ingenious method of calculating the depth of the end-organ and estimated a depth of 0.36 mm. for the thick skin of the palm, and for the forearm one of about 0.17 mm., or less, at about the depth of the bottom of the papillae; after an arbitrary allowance for the threshold stimulus of the end-organ itself, these depths were "corrected" to a depth in the stratum malpighii. Hahn[19] calculated the depth of the cold end-organ, and estimated this in the hand as 0.07 mm. His calculations depend on assumptions of thermal conductivity of skin gaged from in vitro experiments, on a neglect of vascular factors in heat transference, and on a supposed constant blood temperature at a depth of 3 mm. in spite of the observations of Stewart,[20] Zondek[21] and

12. von Frey, M., and Rein, H., in Jadassohn, Josef: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 1, p. 122.

13. von Frey, M.: Ber. d. math- phys. Kl. d. ke. Sächs Gesselsch. d. Wissensch. Leipzig **3**:166, 1895.

14. Strughold, H.: Ztschr. f. Biol. **83**:201, 1925.

15. Waterson, D.: Rep. St. Andrew's Inst. Clin. Research **1**:183, 1922; Brain **46**:200, 1923.

16. Dallenbach, K. M.: Am. J. Psychol. **39**:402, 1927.

17. Ebbecke: Arch. f. d. ges Physiol. **169**:395, 1917.

18. Pendleton, C. R.: Am. J. Psychol. **40**:353, 1928.

19. Hahn, H.: Arch. f. d. ges. Psychol. **65**:41, 1928.

20. Stewart: Heart **3**:33 and 88, 1911.

21. Zondek, B.: München. med. Wchnschr. **66**:1315, 1379, 1919; ibid. **67**:255, 810, and 1041, 1920.

Bazett and McGlone [22] which entirely contradict this last assumption. No reliance can be placed on such calculations. Endres [23] estimated the depth of the end-organ in the forearm by local anesthetization studies as 0.07 mm. and Bazett, McGlone and Brocklehurst [1] (by methods similar to those reported here) assessed the depth in the forearm as 0.15 mm. or less. The results of Endres are convincing. All methods suggest depths of about 0.1 mm., and none exclude Krause's bulbs as the sensory mechanism. Possibly these end-organs lie deeper in the prepuce than in the forearm in spite of the thinness of the epidermis of the former.

Warmth.—The deductions of von Frey [12] that the Ruffini end-organs were responsible for warmth have never been satisfactorily proved. Criticisms of such deductions have been advanced by Waterson,[21] Goldscheider,[24] Ehrmann and Hahn [25] and by Dallenbach.[16] The comments of Waterson and Dallenbach are open to the same criticisms that have been mentioned in the case of cold, and in addition the data of Dallenbach on warmth may also be at fault. His charts show a surprisingly large number of warm spots grouped along definite lines, which may well represent conduction of heat along venous channels such as is here reported; with four stimuli applied to an area of 4 sq. mm. within 12 seconds, such spread would be facilitated by the prolonged temperature change produced by each stimulus (Bazett, McGlone and Brocklehurst [1]).

The depth of the end-organ for warmth in the forearm has been estimated by Endres,[23] by the same method used for cold, as 0.56 mm., a value that agrees closely with that obtained by Bazett and McGlone [22] by calculation from the observed rate of heat penetration in the forearm. The depth has been estimated by Pütter [26] and by Hahn,[27] as 0.1, 0.12 and 0.07 mm. by methods of calculation that have already been criticized in the case of cold. Rein [8] considered their distribution to be related to the anatomic position of nerve trunks.

One serious objection has to be met. The histologic studies of Ruffini [11] demonstrated this end-organ most frequently in the subcutaneous tissue, usually in its more superficial but also in its deepest layers. Ruffini described it as only occasionally present in the dermis (in the fingers) and then in the deeper layers. The depths assigned by

22. Bazett, H. C., and McGlone, B.: Am. J. Physiol. **82**:415, 1927.

23. Endres: Ztschr. f. Biol. **89**:536, 1930.

24. Goldscheider, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 11, p. 131.

25. Goldscheider, Ehrmann and Hahn: Arch. f. d. ges Physiol. **206**:308, 1924.

26. Pütter: Ztschr. f. Biol. **74**:237, 1922; ibid. **86**:89, 1927.

27. Hahn, H.: Arch. f. d. ges Physiol. **217**:36, 1927.

Endres and ourselves in the forearm would give it a more superficial position and the same is true of the present study of the prepuce. The warm spots selected for investigation by ourselves have, however, been those giving the most definite responses and possibly therefore the most superficial present. The diffuse character of the warm spots in comparison with the more discrete localization of cold spots is quite marked even with these relatively small depths, and if these sensations depend on end-organs at a depth of 0.6 mm. or less, it is quite unlikely that Ruffini end-organs situated in the subcutaneous tissue of the forearm could be recognized as discrete sensitive spots. But the presence of such end-organs would readily explain the areas apparently free from warm spots and yet capable of giving diffuse warm sensations when a large applicator is employed, particularly if venous conduction of thermal changes plays an important rôle. The existence of such diffuse sensations has been emphasized by many, by Head,[28] by Waterson,[29] who emphasized the need of a stimulus with an area "as large as sixpence," and by Heilbrun,[30] who obtained sensations without being able to demonstrate with thermocouples any spread of temperature changes to neighboring warm spots. Ruffini end-organs have been demonstrated by Sfameni [31] in the periosteum. If these be end-organs for warmth, the occurrence of sensations of deep origin has to be admitted.

The changes in temperature in the tissues which result from a sudden change in surface temperature have been subjected to mathematical analysis on theoretical grounds by Schmaltz,[32] who described an equation of the probability type and attempted to determine the value of the constants for bone by in vitro experiments. Attempts have been made to adapt his equation to the data here reported, but it cannot be so adapted. However, the equation found to fit the data shows some resemblances to that suggested by him. The apparent shift in the values of the parameters may depend on circulatory adjustments, but the factors are complex. Vasoconstriction to cold might readily decrease the heat capacity and so increase the rate of change on the near surface, and also decrease conductivity and so slow the rate of change on the far surface. Disappearance of the constriction would account for an increased rate of warming in recovery. With a warm stimulus and probable vasodilatation, conditions are more complicated, for an increased blood flow,

28. Head, Henry: Studies in Neurology, London, Oxford University Press, 1920, p. 316.

29. Waterson (footnote 14, first reference).

30. Heilbrun: Deutsche Ztschr. f. Nervenheilk. **101**:290, 1928.

31. Sfameni: Monitore zool. ital. **12**:313, 1901.

32. Schmaltz: Arch. f. d. ges. Physiol. **208**:424, 1925.

besides increasing heat capacity and conductivity, would dissipate the heat over a large area and might itself act as either an additional warming or a cooling factor, according to whether the temperature of the inflowing blood was above or below that of the tissue. Consequently vascular changes might account for the increased rate of change often indicated in the later stages of cold stimulation, as well as for either increased or decreased rates of change which may develop during warm stimulation. The differences in recovery rate demonstrable in figures 5, 6 and 7, are such as might be explained by variations in the vasomotor condition, but this is not warranted since the duration of the stimulus (and the degree of spread of its effects) has a definite effect on the rate of recovery.

CONCLUSIONS

1. A brief preliminary description is given of the various sensory end-organs demonstrable in the prepuce and of their distribution.

2. The spots sensitive to cold in the prepuce and dorsal skin of the penis vary in number from six to twelve per square centimeter. Estimates of their depth from the reaction time and from the rate of thermal transmission suggest a depth of about 0.1 mm. If a thin double fold of skin is obtained, sensitive spots belonging to one layer of skin may be stimulated from either side of the double fold.

3. Histologic studies demonstrate that end-bulbs of the Krause type are distributed in the prepuce, so that their average number is about fifteen per square centimeter, and they have a depth of about 0.1 mm. Many of these occur in groups so that several might be identified as a single cold spot. They lie in the arteriovenous region immediately below the papillae of the corium. Their distribution agrees with that of the cold spots.

4. Spots sensitive to warmth in the prepuce and dorsal skin of the penis are few in number (one or rather less per square centimeter). They may be stimulated from either side of a thin double fold of skin. Their depth may be calculated by comparing the reaction times from the two sides with the rates of thermal transmission, and a depth of 0.3 mm. is thus determined. In a few instances the results appear to indicate a greater depth, in the subdermal tissue at about the center of the fold. These sensory spots are commonly definitely related to visible veins, and spread of thermal changes along the veins is apt to give mild and somewhat diffuse sensations of warmth.

5. Histologic studies demonstrate that Ruffini end-organs have a distribution agreeing fairly well with that of the warm spots. They have a depth of about 0.28 mm. or more and lie in between the second and third venous plexuses of Spalteholz. Some also occur subdermally.

6. In any square centimeter ruled in square millimeters, sixty-two of the squares gave negative responses to touch stimuli when a stimulus slightly above the threshold value was employed. The threshold stimulus has been from 1.5 to 2 Gm. per millimeter radius of the hair employed (0.12 mm. diameter).

7. Nonencapsulated end-bulbs have been identified histologically and are distributed fairly evenly (fifty-two per square centimeter) at a depth of about from 0.03 to 0.04 mm. In a square centimeter the number of square millimeters deficient in this type of end-bulb agreed well with the average number of squares found to be deficient in touch sensation in the physiologic experiments.

8. Some values are given illustrating the character and degree of thermal transmission across a double fold of skin in this area.

Dr. H. Strughold assisted in some of the experiments.

NERVE DEGENERATION IN POLIOMYELITIS

I. VITAL STAINING METHODS WITH NEUTRAL RED APPLIED TO NERVE DEGENERATION *

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In the investigations that form the basis for a series of papers on nerve degeneration in experimental poliomyelitis, of which this is the first, a search was made for a vital dye that would reveal simultaneously changes in the nerve cells of the spinal cord and in the root fibers. Neutral red was found to fulfil this requirement, and the present communication is concerned with a presentation of the methods whereby intravital staining of degenerating nerve fibers may be obtained. Since the course of wallerian degeneration is best known in peripheral nerves severed from their cells of origin, we decided to standardize the methods presented on this basis. It is recognized that modifications may be necessary as needs other than ours become apparent.

A review of the literature shows that since Ehrlich's [1] discovery, in 1886, that methylene blue colors the neuraxon but few additional methods have been forthcoming for the vital staining of nerves. Ten years after the publication of Ehrlich's method, Mayer [2] demonstrated the elective affinity of neutral red for the altered myelin of peripheral nerves undergoing wallerian degeneration. This observation has never been brought forth as a method, and during thirty-five years has gained only casual mention. More recently, the phagocytic cells of degenerating and regenerating peripheral nerves have been studied following intravital staining by trypan blue (Pescatori and Levi [3]).

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* From the Anatomical Laboratories of Washington University School of Medicine.

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1. Ehrlich, P.: Ueber die Methylenblaureaction der lebenden Nervensubstanz, Biol. Zentralbl. **6**:214, 1886.

2. Mayer, S.: Ueber die Wirkungen der Farbstoffe Violett S und Neutralroth, Sitzungs. d. deutschen Naturw. Med. Ver. f. Böhmen, "Lotos" **2**:67, 1896.

3. Pescatori, F., and Levi, M.: Rigenerazione e cicatrizzazione sperimentale dei nervi periferici studiate col metodo della colorazione vitale, Riv. di pat. nerv. **35**:276, 1930.

This tardy accumulation of knowledge concerning the utility of various dyes in the study of living nerve fibers is probably due to the rather general belief that osmic and silver preparations lend themselves best to the study of the structure and relations of the various components of the nerve fiber. That such is not the case is well illustrated by the new knowledge gained by the application of microdissection (de Rényi [4]), ultraviolet rays (Massazza [5]) and polarized light (Baldi [6]) to the vital study of nerve fibers. Just as these methods have yielded fruitful results in the interpretation of the structure of nerve fibers, so vital staining, already introduced for the study of blood (Cowdry [7]), has proved to be of great value.

During observation, by means of vital stains, of the lesions of experimental poliomyelitis in monkeys,[8] it was found that certain changes, obscure or lacking in fixed and stained preparations, were revealed by these methods. They were related to the destruction and removal of the ventral horn cells and repair of the areas of the central nervous system in which the disease had taken hold.

In addition, the motor roots and peripheral nerves of monkeys paralyzed for several days (intravital staining with neutral red) showed colored globules in obviously degenerating nerve fibers. These lesions simulated in degree those found by O'Leary, Heinbecker and Bishop,[9] who used various standard methods to demonstrate histologically the extent of the degeneration in nerves and roots in order to correlate it with deviations from the normal as determined by the cathode-ray oscillograph.

By previous studies it has been found that neutral red colors granules and vacuoles within the living nerve cells and that these may subsequently or independently be blackened with osmium or silver (Covell and Scott [10]). Further, direct observation (from eight to twenty-four

4. de Rényi, G. S.: The Structure of Cells in Tissues as Revealed by Microdissection: II. The Physical Properties of the Living Axis Cylinder in the Myelinated Nerve Fibre of the Frog, J. Comp. Neurol. **47**:405, 1929.

5. Massazza, A.: L'istologia del sistema nervosa alla luce ultravioletta: Nota I. La structura della fibra nervosa a fresco, Arch. ital. di anat. e di embriol. **26**: 89, 1928.

6. Baldi, F.: Ulteriori ricerche a luce polarizzata sulla degenerazione Walleriana, Riv. di pat. nerv. **35**:158, 1930.

7. Cowdry, E. V.: The Vital Staining of Mitochondria with Janus Green and Diethylsafranin in Human Blood Cells, Internat. Monatschr. f. Anat. u. Physiol. **31**:267, 1914.

8. Article V of this series, to be published in the Archives of Neurology and Psychiatry.

9. Article IV of this series, to be published in the Archives of Neurology and Psychiatry.

10. Covell, W. P., and Scott, G. H.: An Experimental Study of the Relation Between Granules Stainable with Neutral Red and the Golgi Apparatus in Nerve Cells, Anat. Rec. **38**:377, 1928.

hours) of the vacuoles and granules selectively colored with neutral red during exposure of the vitally stained cells to osmic acid vapor shows indubitably that when osmication is complete, the interrelation of the various granules has become so altered that their distribution within the living cell can be arrived at only by a study of camera lucida drawings representing graded phases of the process. In a similar way, it might be expected that the condition of myelin in degenerating fibers, vitally colored by neutral red, more nearly approximates the living picture than does that in fibers subjected to preliminary bichromate fixation followed by osmic acid mordanting (Marchi method).

Vital coloration of degenerating nerve fibers by neutral red has other advantages. The method should be as valuable in the rapid examination of the extent and degree of degeneration in other lesions of the central nervous system as it has been in poliomyelitis. Within limits, the degenerative changes that ensue when a nerve trunk is severed, or its cells of origin are destroyed, may be followed to the distribution of the larger fiber bundles.

METHODS

Unilateral section of the sciatic, vagus and radial nerves was aseptically performed under ether anesthesia in seven cats, seven rabbits and nine albino rats. The animals were killed at intervals subsequent to the operations.

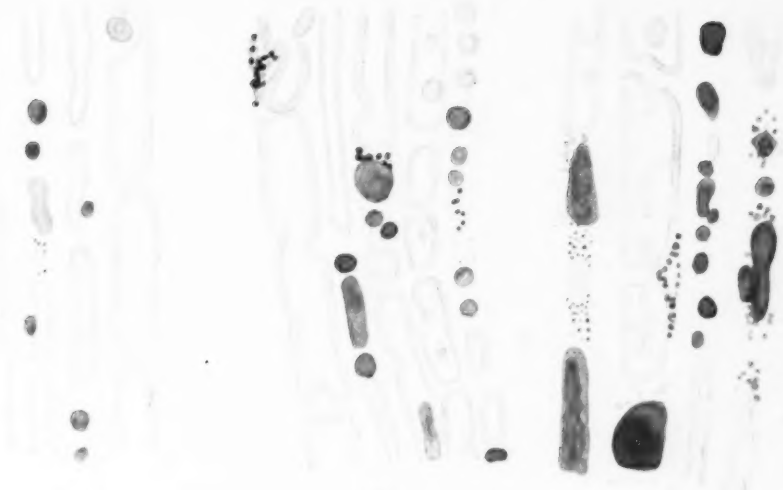
It was found that degenerating nerve fibers could be stained with neutral red by one of three methods: perfusion (Bensley[11]), injection or immersion. The results obtained by the various methods are listed in the table, together with the amounts of dye given, the concentration and the length of time allowed for staining.

Perfusion Method.—The animal was prepared for perfusion according to Bensley's method. The dye was allowed to pass into the aorta for about twenty minutes in each case. The bottle containing the perfusing solution was first raised to a height of approximately 4 feet (122 cm.) and after a few minutes was gradually lowered to 2 feet (61 cm.) at which height it remained during the rest of the procedure.

The stain was made up in 3 per cent acacia in physiologic solution of sodium chloride to a concentration of 1:1,000. Weaker dilutions were found to stain too lightly, while more concentrated solutions stained the degenerating myelin intensely.

Injection Methods.—(*a*) Intravenous Injections: For the intravenous injections of the dye, the cats were anesthetized and the femoral veins were exposed. Under very light anesthesia, varying amounts of different concentrations of the dye were tried. For a medium-sized cat, from 35 to 50 cc. of a 1 or 2 per cent solution gave a moderate intensity of staining after a period of from fifteen to twenty minutes. In rabbits, the dye was injected into the marginal vein of the ear, which enabled us to observe the animals over a comparatively long period of time and to obtain a maximum degree of staining. This was found to be best accomplished by using a 4 per cent solution of neutral red and injecting from 20 to 70 cc. over a period of from one to two hours.

11. Bensley, R. R.: Studies on the Pancreas of the Guinea-Pig, Am. J. Anat. **12**:297, 1911.



Figs 1, 2 and 3.—Reaction to neutral red in interrupted fibers of the cat's sciatic nerve distal to the point of injury. (Magnification, 350 diameters.) The cats received 40 cc. of a 3 per cent solution of neutral red (Grübler) intravenously one-half hour before they were killed. 1. Nerve sectioned four days previously; the small, myelinated fibers show more neutral red stainable myelin than do the larger ones. 2. The nerve sectioned six days previously; as in figure 1, small fibers reveal more degenerating myelin stained with neutral red than do the large ones. However, blocks and droplets of colored myelin are also apparent in the large fibers. 3. Nerve sectioned eight days previously. Increased amount of degenerating myelin which is stainable with neutral red.

Fig. 4.—Interrupted fibers from the peripheral portion of sciatic nerve of cat 3 which received 35 cc. of a 2 per cent solution of neutral red (Krall) intravenously and was then perfused with Ehrlich's vital methylene blue (1,000 cc. of a 1:1,000 dilution). The degenerating myelin colored red, and on exposure to air the methylene blue staining of the axis cylinders also became apparent. Magnification, 1,000 diameters.

Fig. 5.—Interrupted fibers of the sciatic nerve of cat 5, distal to the point of injury, illustrating neutral red staining by the immersion method. Finely teased pieces of nerve were immersed for twelve minutes in a 1:10,000 solution of neutral red (Krall). Magnification, 1,000 diameters.

The results obtained for the cat by this method are illustrated in camera lucida drawings (figs. 1, 2 and 3). When stages three, four and six days following separation of the sciatic nerve are compared, a gradual increase in the amount of myelin stainable by neutral red is apparent, as is evidenced by the illustrations.

Neutral Red Staining of Degenerated Nerves by Various Methods

Animals*	Nerve Sectioned	Time Allowed for Changes	Method and Time of Staining	Amount and Dilution of Dye	Results
Cat 1.....	Right sciatic	4 days	Perfusion 20 min.	1,500 cc. 1:1,000	Moderate degree of staining of degenerated myelin
Rabbit 1....	Right sciatic	4 days	Perfusion 20 min.	1,000 cc. 1:5,000	Degenerated myelin delicately stained; no staining in normal nerve
Rabbit 2....	Right sciatic	4 days	Perfusion 17 min.	1,000 cc. 1:1,000	Intense staining of degenerated myelin
Cat 4 (2 mo. old kitten)	Right sciatic	6 days	Perfusion 26 min.	500 cc. 1:1,000	Moderate degree of staining of degenerated myelin
Rabbit 4....	Right sciatic	6 days	Intravenous 15 min. Perfusion 10 min.	20 cc. 1% 500 cc. 1:1,000	Intense staining of altered myelin
Cat 3.....	Right sciatic	8 days	Intravenous 15 min. Perfusion 20 min.	35 cc. 2% N.R. 1,000 cc. 1:1,000 methylene blue	Degenerated myelin stained red; axis cylinder blue
Cat 2.....	Right sciatic	18 days	Intravenous 10 min. Perfusion 15 min.	12 cc. 4% N.R. 1,000 cc. 1:1,000 methylene blue	Myelin moderately stained; axis cylinder blue; no staining of phagocytes
Cat 7.....	Right sciatic	20 hours	Intravenous 39 min.	50 cc. 4%	Myelin unstained; histiocytes stained throughout nerve; diffuse staining of injured ends of nerve
Rabbit 7....	Right sciatic	72 hours	Intravenous 1 hour	40 cc. 4%	Intense staining of altered myelin in a few small myelinated fibers
Rabbit 5....	Radial and vagus nerves right side	5 days	Intravenous 3 hours	70 cc. 4% solution at intervals of 1 hour	Very intense staining of degenerated myelin
Rabbit 3....	Right sciatic	6 days	Intravenous 16 min.	35 cc. 1%	Moderate intensity of staining
Rabbit 6....	Radial and vagus nerves left side	6 days	Intravenous 2 hours	20 cc. 4% solution at intervals of 1 hour	Moderate degree of staining only
Nine rats...	Sciatic nerve one side	Varying from 4 to 20 days	Subcutaneous or intraperitoneal injections 1-2 hours	10 cc. 4%	Intense staining
Cat 6.....	Right sciatic	8 days	Immersion in 1:100 to 1:10,000 dilutions	.....	1:5,000 and 1:10,000 dilutions stained finely teased preparations in 6 and 12 min., respectively
Cat 5.....	Right sciatic	11 days	Same as above	.....	Results same as for cat 6

* Unless otherwise stated, medium-sized adult animals were used.

In addition, and like the normal control nerves in this respect, the vacuoles and granules of histiocytes and Schwann's cells are colored by the dye. The fiber to the left in figure 3 illustrates the neutral red stainable material of a Schwann's cell.

In a few instances, intravenous injection and perfusion were combined. This insured a satisfactory staining when the animal died soon after the intravenous

procedure. With the perfusion method there was a tendency toward elimination or reduction of the dye in the granules of nerve cells. The ventral horn cells of the cord showed this propensity. It was less marked in the spinal ganglion cells.

Attempts to color both the axons and the degenerating myelin by combinations of stains were successful when neutral red was given intravenously and followed by perfusion with a 1:1,000 dilution of Ehrlich's vital methylene blue in physiologic solution of sodium chloride although there was some tendency toward an overlapping of the two dyes. Figure 4 illustrates the results obtained from such a combination of stains. The myelin that had undergone degeneration was colored red, while the axis cylinders stained blue.

(*b*) Subcutaneous and Intraperitoneal Injections: Subcutaneous and intraperitoneal injections of a 4 per cent solution of neutral red in amounts of 10 cc. were given to rats, and one or two hours were allowed to elapse before the animals were killed. At this time all parts of the body were colored, and the degenerating myelin of the previously severed nerve was stained intensely. Similar results were obtained in one pigeon which had been fed for four weeks on polished rice and exhibited symptoms typical of polyneuritis gallinarum. It received 25 cc. of a 4 per cent solution of neutral red injected into the subcutaneous tissues covering the nerves of legs and wings.

Immersion Method.—Finely teased pieces of degenerating nerves (peripheral stump) and their normal controls were immersed in concentrations of neutral red ranging from 1:1,000 to 1:10,000. The 1:1,000 solution was found to be too concentrated, not only coloring the degenerating myelin, made obvious after the Marchi method of fixation and osmication, but staining unaltered myelin less intensely. This reaction was almost immediate. After six minutes in the 1:5,000 dilution, the degenerating myelin was stained deeply and the normal myelin sheaths were not colored, but after twenty minutes' immersion in this solution, the unaltered sheaths were colored also. The 1:10,000 dilution, stained only the degenerating myelin, provided that the nerve was well teased before immersion, and the results were identical with those obtained by the perfusion and injection methods (fig. 5).

Since there is known to be considerable variation in the staining properties of different samples of neutral red, fourteen lots of the dye were tried. Eleven of these were placed on the market by Grübler and Company, one by the National Aniline Company, one by Coleman and Bell and one by the Laboratories of L. Krall, Boulogne (Seine). None of these failed to stain the altered myelin, but they exhibited a wide difference in toxicity. The most satisfactory for intravenous use were the lots from L. Krall and Grübler and Company, number 0526. For immersion purposes, the neutral red of Krall seemed to give more consistent results.

The preservation of this dye during the processes of fixation, dehydration and embedding, necessary to obtain either paraffin or celloidin sections, presents difficulties. This is particularly true when the material that is colored is soluble in fat solvents. For our own purposes, teasing of the fresh material or frozen sections (cut from fresh material or that fixed for a short period in aqueous chrome sublimate) sufficed. Observations could be recorded immediately and the preparations photographed without delay.

To control these observations which point to the elective affinity of neutral red for the altered myelin of sectioned peripheral nerves, a comparison was made of the effects on both normal and sectioned nerves of crushing, drying and keeping at room temperature or in the refrigerator for varying lengths of time. Thus, when a crushed normal nerve is immersed in a 1:10,000 solution there results immediately a diffusion of the dye throughout its substance. This diffuse staining in the

1:10,000 solution occurs much less readily when normal nerve fibers, not subjected to crushing, are immersed in the same dilution. Desiccation and temperature produce similar diffuse staining. These results may be interpreted as due to the liberation of autolytic ferments by the injured tissue. In sectioned nerves, neither crushing, drying nor prolonged refrigeration was found to alter the selectivity of neutral red for degenerating myelin. On the other hand, if the animal is killed and the sectioned nerve allowed to remain in the body for several hours after death, the degenerating myelin no longer colors red on immersion, but instead appears a murky yellow. Similar results were obtained if an animal into which the dye had been injected intravenously was killed and the nerve was allowed to remain in the body for several hours preceding study.

COMMENT

The particular value of vital staining as applied to wallerian degeneration is made manifest by a recollection of the difficulties that ensue in the interpretation of the results of experimental lesions of the nervous system. Apparently degenerating fibers (Duncan[12]), osmicated globules (corpuscles of Elzholz) and sooty deposits of osmium occur frequently in normal control nerves and in areas of the central nervous system in which no operative trauma has been suspected (Marchi method).

Neutral red, injected intravenously in sufficient quantity, surmounts these difficulties. By coloration of the altered myelin of degenerated fibers before the animal is killed, errors that may accrue from the precipitation of osmium in normal fibers are obviated, since no components of normal nerve besides the finer cytoplasmic inclusions of histiocytes and of Schwann's cells are colored by neutral red. Additional advantages offered by the vital method are the rapid utilization of material and the absence of variation in the quality of the osmic acid and in the procedure of fixation, dehydration and embedding.

A serious disadvantage of the intravital method proposed is the inability to retain permanent preparations of experimental material. This, however, is offset by the stability of the colored myelin for twenty-four hours following removal from the body, a sufficient interval for the obtaining of accurate photographs of the preparations. This relative stability of the dye is most readily explained by contrasting the effect of anoxemia on the neutral red globules in degenerating nerve fibers and cytoplasmic inclusions colored by the same dye. It is well known that dying tissues utilize the available oxygen even to the extent of reducing a complex dye to its leukobase. Within various cytoplasmic inclusions, the dye is offered little immunity from the oxygen needs of the morbid tissues, and the color fades; within the nerve fibers, the fatty base of

12. Duncan, D.: The Marchi Method: A Discussion of Some Sources of Error and the Value of this Method for Studying Primary Changes in the Myelin Sheath, Arch. Neurol. & Psychiat. **25**:327 (Feb.) 1931.

the material colored by neutral red may protect the dye from the oxygen requirements of the tissues, and hence the color is retained for a considerable time even under adverse conditions.

The present state of knowledge concerning the chemical composition of substances for which neutral red is selective should be supplemented by further investigation. This weakly basic dye, by virtue of its ability to diffuse through the cell membrane and its low toxicity, is capable of staining granules and vacuoles of histiocytes, specific granules of islet cells, vacuome, etc. The complex chemical nature of the altered myelin does not permit one to state definitely what substance or substances show an affinity for the dye. Nevertheless, a comparison of the rate and degree of staining with that of other materials in the body tissues that are selectively colored by neutral red reveals the interesting point that myelin, after becoming altered chemically, shows as great, and in many instances a greater, affinity for the dye than do the granules of nerve cells or the engulfed particles of phagocytes. Further, the staining is not likely to fade as rapidly as it does in the cytoplasmic granules, and there are also present varying degrees of staining of blocks of altered myelin. The latter observation cannot be interpreted as due to a lack of penetration of the dye, but instead illustrates the point that some parts of the myelin sheath are less advanced in degeneration than others, and the dye brings out these progressive changes.

CONCLUSIONS

Neutral red is a selective vital stain for degenerating myelin and may be applied by perfusion, injection and immersion. The merits of these new methods are discussed. They form a valuable adjunct to the Marchi and Weigert procedures for the study of wallerian degeneration.

NEUROLOGIC PROBLEMS IN CHILDHOOD*

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The managers of the Children's Hospital, with the generous support of the Julius Rosenwald Fund of Chicago, have established a ward for the study of neurologic problems among children, which has been in operation for a year. Obviously we have no important statistics to offer, but we are eager to present our plans and methods for discussion. It is particularly interesting to us to find out whether pediatricians, coming without formal training into the highly sophisticated specialty of neurology, can suggest new problems or at least find out whether shifts of emphasis are desirable. The grounds for discontent with the conventional method of approach and the selection of our tentative program seem to us logical.

This hospital, like many others, is a relatively old institution with an established clientele, so that abundant material is available. For many years, skilful neurologic consultation service has been given and an adequate outpatient service has been available. In the wards, surgical, orthopedic and medical services were carrying on their work with entire adequacy.

Under such a regimen, a considerable proportion of the neurologic patients encountered in the hospital have been well cared for. The medical service supervised cases of acute infection and tetany and other urgent problems. The orthopedic service took charge of the later phases of infantile paralysis and has done what it could for the mechanical difficulties, such as deformities, that occur in cerebral palsies. The surgical service had in charge such conditions as cerebral tumors, cerebral abscesses, and the like. Obviously, we have been intelligent enough to utilize our neighbors' skill and equipment when we have had any doubts about our own competence.

An outpatient staff could be depended on to do intelligent work in recognizing the conventional syndromes of deterioration.

With all this competent machinery and personnel, however, it was clear that we needed a new type of equipment. If we accept the idea that any permanent disability in a young child forces modification of

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* From the Medical Service of the Children's Hospital and the Department of Pediatrics, Harvard Medical School.

educational routine, it is clear that observation should involve study of activity and reaction to educational opportunity. The ordinary hospital routine, of course, abolishes activity and ignores education.

With this idea in mind we have worked out a fairly definite plan. We are attempting to appraise the results of fixed lesions of the central nervous system and to supervise educational plans. In doing this the medical staff frankly is entering, without adequate training, the field of education, but I think that we are doing so with intelligent humility.

Of course, plans for education depend on an understanding of the intact physiologic assets rather than on the deficit represented by the lesion. The physician, therefore, is forced to formulate as adequate a conception as he can of the physiologic residue. Naturally, a sensible preliminary step is to attempt to establish the presence or absence of marked anatomic defects. We have concluded that encephalography is almost without danger in these cases, and we include its use in most cases as a part of an adequate physical examination.

The strictly medical contribution is largely confined to appraisal of motor assets, with occasional recognition of gross sensory defects. If this part of the human machine can be utilized, it becomes essential to get as clear an idea of the intellectual assets as possible.

Dr. Elizabeth Lord, psychologist of the unit, has accepted a very complicated challenge. It is not necessary to emphasize that the diffuse lesions responsible for the disabilities manifested by children with cerebral palsies produce disorders of speech and disorganization of motor patterns that make all the conventional batteries of physiologic tests useless for these subjects. In spite of that, Dr. Lord has found ways to get around most of the difficulties so that levels can be found.

If we form a tentative opinion that the total physiologic assets and the intellectual level justify an attempt at education we start on a regimen that is not as simple as it sounds. Physical therapy, hydrotherapy, nursery school work, tutoring, organized play, etc., are carried on in the presence of uniformed nurses, and the whole process is ultimately controlled by a board of managers who have been taught that isolation and the prevention of cross-infection are fundamentally important.

Every one is cheerfully and often vigorously anxious to get more time for his or her special job. The physical therapist is sometimes astonished by the placid attitude of the nursery school supervisor; the nursery school teacher tries to protect the children against the routine to which nurses are accustomed. Out of this constructive chaos we are gradually emerging. On the whole we are finding that it is entirely possible to conduct acute educational experiments. Many of the problems are psychologic in nature. Reading disabilities, speech disorders,

etc., are the rule rather than the exception. "Cerebral palsy," though a convenient term, gives no real picture of the condition it names.

The majority of our children are below school age. This adds to our troubles in some ways. It is easier, of course, to appraise a residue if we have a known total from which to subtract. In ordinary adult practice we are dealing with subtraction from a known quantity and quality of behavior units. With little children, particularly if the disability has existed from birth, we learn to make allowances for the very important element of growth. Reeducation is the aim among adults, but education of a primary nature is needed among children.

Any difficulties of this sort are, we all believe, more than counterbalanced by favorable factors. In the first place, the children are not people who are necessarily condemned to a lower level of behavior than they have previously enjoyed. On the whole, if they can be helped they are placed on a level that increases their activity beyond their previous experience. Moreover, we are judged on a different "time table" than are practitioners among adults. A period of months or years is almost intolerably long for medical treatment. On the other hand, it is normal if education is the aim.

As far as I know there is not a single new thing about this unit. Medicine, psychology, education and the rest have worked together on this problem of the handicapped child in many places. It seems to us, however, that the acceptance of this combination by the managers and the staff of a hospital devoted to acute organic disease is an interesting development.

After a year's work we are convinced that it is entirely possible to attempt to put diagnoses into a form that indicates the intact physiologic residue, to formulate the prognosis in educational terms and, in favorable cases, to prescribe and try out an adequate educational routine.

In a hospital it is probable that medical attitudes must control, but it is evident that the doctor must walk humbly and warily lest he attempt to dictate educational policy and be found wanting. With eager and not too pliant associates, the pediatrician with neurologic interests finds that these patients, usually regarded as hopelessly handicapped, present a series of problems in physiology and education of extraordinary interest. Many of the difficulties that we are finding among children with disorders of the nervous system also occur in patients with damaged hearts, arthritis, diabetes and other conditions. It seems reasonable to suppose that some such cooperative enterprise of doctors and teachers would be of value in all cases in which prolonged disability threatens education.

ABSTRACT OF DISCUSSION

Dr. Bernard Sachs, New York: I wish to congratulate Dr. Crothers on the opportunity that he has for the special investigation of diseases of the nervous

system, and I am glad to know that he has started on such a sensible basis. The only other institution that I know of that is at all comparable to this is one that has been established in Leningrad.

Are you limiting the age of the children under treatment?

DR. CROTHERS: By the traditions of the hospital we are limited more or less to children under 12 years. In practice, by the application of a little pressure, we can always secure admittance for children up to the age of 15, and, having admitted them up to that age, it is extremely difficult to refuse to care for them if they are a little bit older, so that it is possible to take children up to adolescence. Officially, however, we take them up to the age of 12 without protest. Of course, it is a great deal simpler to use groups of about the same age at about the same time, and this service being a part of a very large general children's hospital, it is always possible to keep this particular unit free for a particular group of patients. We do not have to deal with patients with hydrocephalus, encephalitis, etc., in beds one after another. We can get a relatively small number of beds with cases that we are particularly interested in at the moment. We have little responsibility and a great deal of freedom.

DR. ISRAEL STRAUSS, New York: When you have determined the intellectual level, physical condition, etc., and decide to send a child home, if the mother is not competent to follow out your routine, how to you get the personnel for follow-up treatment? Do you train the workers in the institution?

DR. CROTHERS: If a child is going to present a problem over a period of years, and if there is a place to which people can come and get what we have to offer, I am not sure that it is either wise or feasible to establish a general training school, aside from the fact that all our nurses go through training for this work. If people want a specially trained nurse, they can get one without trouble. Our responsibility, as I see it, ends in making logical and intelligent plans and presenting them so clearly that the family can usually be made to see the adequacy of them.

DR. HARVEY CUSHING, Boston: What selected cases are you making the source of your primary study?

DR. CROTHERS: It happens that we are dealing chiefly at the moment with the cerebral palsies, above the level that would probably place the child in the state schools and below the level that will enable the child to get into the ordinary grade schools without any difficulty; that is, we are accepting a group of cerebral palsies (in children) between 2 and 16 years of age.

DR. COLIN K. RUSSEL, Montreal: Do you have an ambulance service to bring these children to the school daily?

DR. CROTHERS: We do not have an ambulance service but, with the aid of the outpatient department and the Red Cross we are able to bring the children in fairly adequately. We have not yet attempted to organize (and I am not perfectly sure that we shall) along definite educational lines. What we hope to do more than anything else is to formulate certain difficulties and certain deficits in the state procedure and in the ordinary educational procedure, and demonstrate the need of certain facilities as sufficient cases develop. For instance, I think it must be evident that there is no provision for the education of an athetoid child of good intelligence. There are a number of gaps of that sort which I think are not filled partly because it has not been proved that there are enough cases to justify such special provision. We are frankly groping; we have no formulas at all. As I say, we are learning to be teachers, and it is difficult.

PROGRESSIVE FACIAL HEMIATROPHY

REPORT OF THREE CASES *

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AND

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Originally described by Romberg in 1846, and for this reason likewise known as Romberg's disease, progressive facial hemiatrophy has since aroused the interest of clinicians practically in every part of the world and furnished the theme for a large number of publications. Important monographs ** on the subject have been written by Möbius,[1] Cassirer [2] and Marburg,[3] and more than 25 theses have been devoted to it in France and Germany alone, that by Korn [4] being unquestionably one of the most remarkable. The condition receives rather scant attention in most textbooks on neurology, the most notable exception being Oppenheim's [5] famous Lehrbuch, in which it was accorded a lengthy and exceptionally instructive description. In recent years, probably the most noteworthy contribution on facial hemiatrophy is that by Wartenberg,[6] which appeared in 1925. The older literature has been com-

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** As it does not seem either practical or useful to incorporate in this article the entire bibliography of facial hemiatrophy, most of which has been thoroughly listed by Cassirer, Marburg and Wartenberg, the references given in our paper, unless designated by an asterisk, apply to contributions not found in the works of these authors and to articles published since 1924.

1. Möbius: * Der umschriebene Gesichtsschwund, in Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1895, vol. 11, pt. 2.

2. Cassirer: * Die vasomotorisch-trophischen Neurosen, Berlin, S. Karger, 1912.

3. Marburg: * Die Hemiatrophia facialis progressiva, in Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1912, vol. 11, pt. 2.

4. Korn, R.: * Ueber Hemiatrophia faciei progressiva, Inaug. Dissert., Berlin, 1910.

5. Oppenheim: * Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 2166.

6. Wartenberg: Zur Klinik und Pathogenese der Hemiatrophia faciei progressiva, Arch. f. Psychiat. **74**:602, 1925.

pletely indexed by Cassirer and particularly by Otto Marburg, and the appended bibliographies of the combined monographs of these authors, both of which appeared in 1912, contain 248 references. In Wartenberg's article, 54 additional references are listed year by year. From 1900 to 1925, we have found 23 titles apparently overlooked by the preceding authors, and from 1925 to the present time we have collected the reports of 40 cases, which brings the total to 365 references. As the works of Oppenheim and Cassirer and a fair number of articles prior to 1925 are based on the observation of more than 1 case, sometimes as many as 5 cases, and, further, as in all probability we, like others, have overlooked a number of references, we feel certain that the total number of reported cases of facial hemiatrophy easily reaches the figure of 400 and probably exceeds it.[7] It is therefore evident that this condition, reputedly rare, is far less so than is generally believed.

GENERAL DESCRIPTION

From the classic descriptions of Möbius, Oppenheim, Cassirer and Marburg, a preliminary portrayal of progressive facial hemiatrophy may be attempted and the salient features of the condition defined, subject to critical revision in the light of many important facts brought out in the more recent literature. The earlier writers held that the condition affected chiefly females (two thirds of the cases) and that the left side was involved in the majority of cases. In the literature that has appeared since 1912 we have found no material difference in incidence between the sexes and no significant predominance of left-sided over right-sided hemiatrophy. The condition is definitely a disease of early life and particularly of the second decade, but cases have had their onset in the first years of life, some of them being apparently congenital or due to birth trauma. Under this heading Marburg mentioned the cases reported by Elder, Huber, Mauclaire and Hrach. Likewise, in a considerable number of cases, facial hemiatrophy has appeared in middle and even in advanced life. Wartenberg mentioned Stiefler's case which developed at 54, Haenel's case at 47, one of Weinberg and Hirsch's cases at 44 and Frankl-Hochwart's case at 37. To these we are able to add the case of Ascher[8] with its onset at the age of 43, that of Kurt Mendel[9] at 51, that of Stief, Sándor and Tanka[10] at 64,

7. Deleted.

8. Ascher: Ein Fall von Halsrippe, Arch. f. Psychiat. **41**:1127, 1906.

9. Mendel, Kurt: Demonstration eines Falles von Sympathicuslähmung durch ossificierte Struma, Arch. f. Psychiat. **41**:1112, 1906.

10. Stief, Sándor and Tanka: Seltener Fall von Hemiatrophia faciei, Orvosi hetil. **69**:459, 1925; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:649, 1925.

that of Léri [11] at 28, that of van Bogaert and Helsmoortel [12] at 74, that of Hanse [13] at 51, that of Ziegler [14] at 36 and that of Trepte [15] at 41. It is obvious, therefore, that no age is exempt from facial hemiatrophy.

As a rule, the atrophic process involves all the structures of the face: the skin, subcutaneous fat and connective tissue, muscle and bone. That the skin may escape entirely or that the subcutaneous fat and connective tissue may disappear before or without concomitant involvement of the skin has been emphasized by Marburg and Wartenberg, in whose combined statistics fully 15 such cases are mentioned. As regards the so-called muscular atrophy, Marburg correctly pointed out that the atrophy is due essentially to the disappearance of the fatty and connective tissue components of the muscle, as is well shown by the retention of functional activity and the absence of qualitative changes in the electrical reactions. This is true not only of the masticatory and facial muscles but also of the lingual and palatal musculature, which not uncommonly participates in the hemiatrophy. The cartilages are involved in the following order of frequency: nasal, auricular, laryngeal and tarsal. While atrophy of the nasal cartilage is common enough, the other cartilages are rarely altered. Involvement of the cartilage of the ear has been observed in only 3 cases, those of Körner, De Maire and Huber, according to Marburg and Wartenberg. The latter author likewise stated that the larynx or trachea participated in the hemiatrophy in the cases reported by Harbitz, Körner and Schlesinger. A similar case has recently been reported by Borowsky.[16] As to the wasting of the bony element, it has been emphasized by Cassirer, Marburg and others that it is directly proportional to the age period at which the hemiatrophy has its onset and that the pronounced atrophy of bone is not surprising in a process electively affecting young persons before full development of the bony framework has been reached. Marburg mentioned Rothmann's case as apparently the only exception

11. Léri, A.: Sur la dissociation du réflexe oculo-cardiaque et des épreuves pharmacologiques dans l'exploration du sympathique, Rev. neurol. **33**:1092 (June) 1926.

12. van Bogaert and Helsmoortel: Syndrome paratrigéminal du sympathique oculaire: Hémiatrophie faciale, J. de neurol. et de psychiat. **27**:222, 1927.

13. Hanse, A.: Halbseitige vegetative Störungen (Hemitetanie, Hemiatrophia faciei), Klin. Wchnschr. **6**:2453, 1927.

14. Ziegler, Lloyd H.: Lipodystrophies: Report of Seven Cases, Brain **51**: 147 (June) 1928.

15. Trepte: Hemiatrophia totalis mit Sclerodermie und Sympathicus-Operation, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:809, 1930.

16. Borowsky, M.: Ein Fall von Hemiatrophia facialis progressiva mit halbseitiger Hypoplasie des Rachens und Kehlkopfes, Sovrem. psikhonevrol. **1**:121, 1925; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **43**:560, 1926.

up to the time of his monograph. However, among the cases previously mentioned in connection with the occasional tardy incidence of facial hemiatrophy, pronounced involvement of the bones was present in the observations of Kurt Mendel[9] and Stiefler,[17] and atrophy of the bones of the face in cases developing after the age of 20 was specifically mentioned by Boguslawski,[18] Krueger,[19] Roger, Reboul-Lachaux and Montagnier,[20] L. Cerni,[21] Mauthey[22] and H. G. Wolff.[23]

Facial hemiatrophy may begin at any point, such as the region of the orbit, about the angle of the mouth or the wing of the nose, over the malar prominence or along either the vertical or the horizontal segment of the mandible, and more rarely in the upper part of the neck (the domain of the second and third cervical roots). From the initial point of invasion the atrophic process may either gradually or rapidly spread until the entire half of the face is involved, or it may come to a standstill spontaneously at any stage of its evolution. In the latter case we have the focal or circumscribed atrophies which in some instances seem to correspond to the distribution of one or another of the three divisions of the trigeminal nerve, while in the former case the generalized facial hemiatrophy produces such a startling asymmetry that the two sides of the face appear to belong to entirely different persons. It is well known, and the fact has been particularly stressed by Oppenheim, Cassirer, Wartenberg and Mankowski,[24] that the atrophy in many cases extends far beyond the trigeminal innerva-

17. Stiefler: * Ein Fall von posttraumatischer Hemiatrophia faciei progressiva im vorgeschrittenen Alter nebst Bemerkungen zur Pathogenese, Ztschr. f. d. ges. Neurol. u. Psychiat. **88**:305, 1924.

18. Boguslawski: Hémiatrophie faciale droite précédée par l'apparition précoce de névralgie dans la région du premier rameau de la V^e^ paire, Rev. neurol. **34**:135 (July) 1927.

19. Krueger: * Ein Fall von Hemiatrophia faciei mit Sensibilitätsstörungen und gleichzeitiger tonisch-clonischen Kaumuskelkrämpfen, Neurol. Centralbl. **35**: 17 (Jan.) 1916.

20. Roger, Reboul-Lachaux and Montagnier: Syndrome de Claude Bernard-Horner et hémiatrophie faciale dans un cas de syringomyélie fruste, Rev. neurol. **34**:555 (April) 1927.

21. Cerni, L.: Zwei Fälle von Hemiatrophia unilateralis totalis, Sovrem. psikhonevrol. **3**:494, 1926; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **46**: 597, 1927.

22. Mauthey, Paul: Hemiatrophia faciei dextra nach Strumektomie, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:192 (April) 1928.

23. Wolff, H. G.: Progressive Facial Hemiatrophy: Report of a Case with Convulsions and Anisocoria, J. Nerv. & Ment. Dis. **69**:140, 1929.

24. Mankowski: Zur Pathogenese der Hemiatrophia facialis: Ein Fall von symptomatischer Hemiatrophie nach Encephalitis epidemica, Arch. f. Psychiat. **78**:572, 1926.

tion zone, and it occasionally spreads to the neck, thorax and arm or even to the entire half of the body, constituting what is known as total hemiatrophy. Cases coming under the latter heading are, however, comparatively rare. In the combined monographs of Cassirer and Marburg we found 12 cases listed as instances of complete unilateral atrophy (the cases of Afzelius, Elder, Henschen, Hrach,[25] Knapp,[26] Lunz,[27] E. Mayer, Nixon, Orbison, Pelizaeus, Raymond and Sicard,[28] and Steven[29]). In his article Wartenberg mentioned a few of the foregoing and added the cases of Cassirer[30] and of Geist.[31] Since 1924, we have found references to 9 additional cases, those of Stief, Sándor and Tanka,[10] L. Cerni[21] (2 cases), Popova,[32] Norman Tobias,[33] J. J. Eller,[34] Boardman,[35] O'Leary and Nomland[36] and Trepte.[15] Apparently, then, about 23 cases of total hemiatrophy have been reported up to the present time. It is questionable whether Boardman's case belongs in this group:

His patient developed, at the age of 7½ years, a definite facial asymmetry and then began to limp with the right leg; soon a total right-sided atrophy was manifest. There was a difference between the two sides as regards surface temperature, perspiration and vasomotor activity. Measurements showed that the long bones on the right side were shorter than those on the left, and that the circumference of the right arm and leg was likewise less than that of the left.

25. Hrach: * Ueber einen Fall von angeborener neurotischer Gesichtsatrophie, Wien. med. Wchnschr. **54**:343, 1904.

26. Knapp, P. C.: * Case of Hemiatrophy and Scleroderma, Boston M. & S. J. **64**:671, 1911.

27. Lunz: * Hemiatrophia totalis cruciata, Neurol. Zentralbl. **15**:1045, 1896.

28. Raymond and Sicard: * Trophonévrose hémiatrophique totale et familiale, Rev. neurol. **10**:593, 1902.

29. Steven: * Case of Scleroderma with Pronounced Hemiatrophy of the face, Glasgow M. J. **50**:401 (Dec.) 1898.

30. Cassirer, R.: * Die vasomotorisch-trophischen Neurosen, in Lewandowsky: Handbuch der Neurologie, Berlin, J. Springer, 1914, vol. 5, p. 236.

31. This reference does not appear in Wartenberg's bibliography, and we have not found it in the numerous publications available in the New York State Medical Library.

32. Popova, N.: Pathologie und Therapie der Hemiatrophia faciei et corporis, Sovrem. psikhonevrol. **4**:475, 1927; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:338, 1927.

33. Tobias, Norman: Extensive Linear Nevus with an Associated Hemiatrophy, Arch. Dermat. & Syph. **18**:451 (Sept.) 1928.

34. Eller, J. J.: Scleroderma and Facial Hemiatrophy, Arch. Dermat. & Syph. **18**:766 (Nov.) 1928.

35. Boardman, W. P.: Total Hemiatrophy with Scleroderma, Arch. Dermat. & Syph. **15**:504 (April) 1927.

36. O'Leary and Nomland: Study of One Hundred and Three Cases of Scleroderma, Am. J. M. Sc. **180**:95 (July) 1930.

Sclerodermal thickening of the skin was limited to the right lower extremity. It is stated that all the tendon jerks were more active on the right, which likewise presented a typical ankle clonus and Babinski phenomenon.

It is well known that in infantile hemiplegia the paralyzed limbs often remain stunted in growth, that the shortening may eventually amount to 6 cm. or more in the upper extremity and to 3 cm. in the lower extremity, that facial asymmetry is common and that this unilateral atrophy involves all the tissues. It is our impression that Boardman's case may have been of this type. The same apparently applies to the cases reported by Elder and by Orbison. If it were proper to include under the heading of total hemiatrophy all the cases of infantile cerebral hemiplegia exhibiting this feature, it is obvious that the number of such cases would assume incredible proportions. The fact of such an occurrence is none the less of great interest, as it demonstrates the influence of the higher nerve centers and tracts on the trophism of the various tissues, and it is certain that relative or even pronounced functional inactivity alone cannot account for the frequently massive disproportion between the two sides of the body. In the group of total hemiatrophy, unquestionably the most interesting is the celebrated case of Lunz [27] in which a left-sided facial hemiatrophy was combined with a right-sided atrophy of the extremities, thus realizing in the domain of the vegetative nervous system a syndrome comparable to the alternating or crossed hemiplegia known as Millard-Gubler's syndrome. A case somewhat resembling Lunz' case is that recently reported by Léri.[11]

A woman, whose symptoms began at the age of 28 with neuralgic pains in the left trigeminal distribution, presented a left-sided facial atrophy involving more especially the skin, subcutaneous tissue and musculature, combined with weakness and atrophy of the right arm. In addition there were an incomplete paralysis of the motor oculi and abducens on the left side and a discrete lingual hemiatrophy on the same side. Finally, perspiration was much more abundant on the left side of the face than on the right, and the hair of the left side of the head was scantier and showed a tendency to premature grayness. Léri incriminated involvement of the sympathetic centers and pathways for the various features (other than the paralytic) observed, and, in the absence of syphilis, syringomyelia and epidemic encephalitis, postulated a diagnosis of chronic polio-encephalomyelitis of unknown etiology. Incidentally, he called attention to the practically negative results obtained with the various pharmacologic tests (epinephrine, atropine, pilocarpine) and therefore stressed the dissociation of the obvious sympathetic disturbances and the oculocardiac reflex, which was extremely pronounced, on the one hand and pharmacologic reactions on the other.

It is admitted, of course, that this case is an instance of what Marburg and Wartenberg would designate as a symptomatic crossed hemiatrophy. Although not at all a case of alternating hemiatrophy,

a most interesting instance of crossed vegetative disturbance was reported by Volhard.[37] His patient presented, aside from a left facial hemiatrophy, brown pigmented areas scattered over the right side of the body, on the neck, chest, abdomen, arm and leg. Trepte[15] made the statement that most cases of complete hemiatrophy are associated with scleroderma, but this surely does not apply to the cases of Elder, Hrach, Orbison, Raymond and Sicard, Popova and Norman Tobias or to L. Cerni's case 1. Finally, facial hemiatrophy may spread to the other side of the face, thus realizing what has been called double facial hemiatrophy or bilateral facial atrophy. Up to 1912, Marburg collected 23 such cases from the literature, and in 1925 Wartenberg added 3 cases (Curschmann, Boenheim and Hübner). Since then we have found but 1 additional case, case 4 in Sterling's[38] communication on facial hemiatrophy of infectious origin, thus bringing the total number to 27.

Falling out or blanching of the hair of the eyebrow, eyelashes, beard or forehead has been stressed by a number of authors, and Marburg further stated that this was the initial manifestation in the cases reported by Claude and Sézary, Beer, Stepp and Wechselmann. Oppenheim originally claimed that the hair of the scalp was almost never involved, but alopecia areata was present in Rosenthal's case[39] and an early manifestation in Klingmann's case.[40] It antedated all other manifestations in Wartenberg's case as well as in our case 3. The occurrence of pigmentary anomalies (achromia or hyperchromia, vitiligo) is not particularly uncommon, while herpes and pigmented nevi or telangiectases are rare. Recurrent herpes in the distribution of the second or maxillary division of the trigeminal nerve was present in the case of Wilfred Trotter,[41] and pigmented nevi were described by Wartenberg in his case. In Norman Tobias' case,[33] one of congenital right-sided ptosis and total left-sided hemiatrophy, an extensive nevus of mixed verrucous and pigmentary type involved the left side of the head, face and neck as well as the tongue and buccal mucosa

37. Volhard: * Fall von Hemiatrophia facialis mit gekreuzter Pigmentation am Rumpf, Deutsche med. Wchnschr. **29**:280, 1903; Ueber chronische Dystrophien und Trophoneurosen der Haut, München. med. Wchnschr. **50**:26, 1903.

38. Sterling: Hémiatrophie faciale d'origine traumatique, Rev. neurol. **34**:138 (July) 1927.

39. Rosenthal: * Ueber einen Fall von partiellen Sklerodermie mit Übergang in halbseitige Gesichtsatrophie kombiniert mit Alopecia areata, Berl. klin. Wchnschr. **34**:755, 1889.

40. Klingmann, T.: * Facial Hemiatrophy: Statistical Review of Etiologic Factors and Pathogenesis: Report of a Case with Morphologic Stigmata, J. A. M. A. **49**:1888 (Dec. 7) 1907.

41. Trotter, W.: Recurrent Herpes Zoster of the Face with Facial Hemiatrophy, Proc. Roy. Soc. London (Sect. Dermat.) **9**:43 (Dec.) 1915.

and ended abruptly at the midline. The midline of the palate was occupied by a verrucous ridge which extended posteriorly to the bifid uvula. The secretory functions (sweat and sebaceous glands, lacrimal and salivary glands) do not show uniform behavior. Oppenheim believed that sweat was usually increased, whereas Marburg stated that when the sudoral function is altered it is more commonly diminished, while the lacrimal secretion is increased. We found the greatest variations in this respect in the available literature. The same is true of the surface temperature and, although Marburg stated that it is more frequently lower on the affected side, there are some cases in which it is definitely higher and a large number in which no appreciable difference can be detected between the two sides. Although atrophy of the vasculature is difficult to demonstrate, it is to the presumed narrowing of the vessels that the frequently abnormal pallor of the skin on the affected side is to be attributed. It was mentioned by Marburg that Bouveyron, Bergsohn and H. Wolff all claimed a definite narrowing of the carotid and temporal arteries in their cases. A notable exception to this array of conflicting observations is the interesting case recently reported by Mankowski.[24]

> This concerns a man, aged 23, in whom a right facial hemiatrophy apparently followed an attack of epidemic encephalitis. The patient complained of marked salivary and lacrimal secretion as well as of an excessive discharge of mucus from the right nostril. The right side of the face and right ear were hyperemic. Perspiration was more marked throughout the entire right side of the body, but the difference was most striking over the head, face, neck and breast. An artificial increase in temperature markedly accentuated the sudoral asymmetry. Dermographism was more intense and persistent on the right than on the left, and the surface temperature (cheek) registered 35.8 C. (96.4 F.) on the right against 33.6 C. (92.5 F.) on the left. Horner's syndrome was present on the right. Otherwise the results of examination were strictly negative, motor, striatal and other signs being entirely wanting. Mankowski nevertheless postulated a lesion of the floor of the third ventricle and regio hypothalamica.

Mankowski's interpretation is difficult to understand. A lesion or scattered small foci at the pontobulbar level involving the sympathetic and parasympathetic centers or pathways (such as the nucleus salivatorius of Kohnstamm, the descending connections of the nerve of Wrisberg, the oral extremity of the fasciculus solitarius, etc.) would, we believe, offer a more logical explanation of the clinical observations. It is interesting to note, moreover, that in Mankowski's case the picture of a vegetative disorder is practically the reverse of that observed in connection with the syndrome described by Madame Dejerine-Klumpke and known as the Klumpke syndrome in which, as the result of traumatic avulsion (at birth or under other circumstances) of the last cervical and first thoracic roots, in addition to the motor paralysis of

the hand and part of the forearm one finds, on the corresponding side, a classic group of sympathetic disturbances consisting of Horner's oculopupillary syndrome, pallor of the face and neck, unusual dryness of the nostril and mouth, and diminished sweating over the face, neck, arm and chest. Facial hemiatrophy is not an invariable accompaniment of the Klumpke syndrome, but has been observed in a considerable number of cases as will be pointed out later. We believe that it probably occurs only in cases in which the efferent preganglionic fibers coursing in the involved roots have not been completely severed. Returning to Mankowski's case, while we have no intention of suggesting a lesion of the lower cervical cord as the basis of the clinical picture, we do believe that his localization is unwarrantedly high, and we do not recall any observation of Horner's syndrome in lesions above the metencephalon.

So-called neuralgic pains are common and may develop at the same time as the atrophy or appear at any stage of its evolution, but in a fair proportion of the cases reported the pain preceded the atrophy by several months or even years. This was notably so in the case reported by Boguslawski,[18] and seems to occur particularly in those instances in which the process is fairly limited to the area of distribution of one or more branches of the trigeminal nerve, as in the cases of Stiefler,[17] van Bogaert [12] and Souques and Bourguignon [42] and in cases following facial trauma. In the earlier editions of his textbook, Oppenheim stated that the hemiatrophy was usually preceded by neuralgic pains in the affected half of the face. This opinion no longer holds true, and a survey of the more recent literature shows that pains are as frequently absent as present. Objective sensory disturbances are wanting in the great majority of cases, but there are several authentic cases on record in which they were definite and even pronounced. The more detailed consideration of trigeminal as well as of oculopupillary manifestations will be taken up under the heading of pathogenesis.

REPORT OF CASES

Case 1.—*History.*—M. H., a white woman, aged 20, was admitted to the Albany Hospital on Feb. 5, 1930, complaining of facial asymmetry. About three years before, she had received a vigorous blow over the right cheek, having been accidentally struck by the fist of a relative. Approximately two weeks later, the patient noticed that the tissues of the cheek were beginning to "sink in." The wasting gradually increased and extended to adjacent regions of the same side of the face until about one year prior to the date of admission, since when the process apparently had remained stationary. No mention was made of neuralgic pains or other subjective discomforts in the affected region of the face. The past

42. Souques and Bourguignon: Un cas d'hémiatrophie progressive de la face améliorée par l'ionization calcique, Rev. neurol. **29**:204 (Feb.) 1922.

history revealed that she had had a number of infectious invasions: measles at 5 years, lobar pneumonia at 8 and an acute arthritis involving both ankle joints approximately two years later. Moreover, at the age of 6 years, she had an attack of chorea which lasted about two months; since, she had remained more or less nervous and unstable. Although no further arthritic manifestations appeared, she had repeated attacks of acute tonsillitis, and several years before admission a peritonsillar abscess developed on the right side. Menstruation began at the age of 15 and had always been regular and normal in amount. Aside from the traumatism previously mentioned, the patient had never sustained any injury or undergone any surgical operation about the neck, face or head.

Examination.—With the exception of the right side of the face and neck, a general physical examination gave entirely negative results. The thoracic and abdominal viscera, the somatic musculature and the tendon and cutaneous reflexes

Fig. 1 (case 1).—*A*, definite and generalized facial asymmetry and decided reduction of lateral segment of eyebrow. *B*, triangular depression in mandibular region as well as marked depression of frontotemporal region.

exhibited no variation from the normal. Blood pressure readings were 130 mm. systolic and 80 mm. diastolic.

The facial asymmetry was definite and striking, the right side of the face being plainly less full than the left (fig. 1). The most pronounced defect occupied the lateral segment of the cheek and took the form of a triangular depression with its apex directed toward the angle of the mouth while the base extended posteriorly and laterally over the vertical ramus of the mandible and embraced the parotid and submaxillary regions (thus reaching well within the radicular distribution of the second and third cervical nerves). In addition, another depression, of lesser degree, occupied the right temporal region and outermost segment of the forehead, forming a rhomboidal zone which narrowed down toward the external angular process of the frontal bone. The atrophic process involved the skin, subcutaneous fat and connective tissue as well as the underlying bone. In the affected regions the skin was thinned, smooth, moist, elastic and freely movable. Nowhere did it show adhesions to deeper lying structures or exhibit sclerodermal

characteristics. There was likewise no evidence of either achromia or hyperchromia. The hair of the right eyebrow was distinctly scantier than that of the left, the loss being especially noticeable in the lateral segment. There were no objective sensory losses in the domain of the right trigeminal nerve. While the muscles of mastication on the right side showed unquestioned reduction in bulk, they retained normal vigor, and functional tests revealed no apparent difference between the muscle groups of the two sides. All the muscles supplied by the upper and lower branches of the right facial nerve appeared entirely normal as regards tone and motor strength. Moreover, despite the patient's extreme intolerance to electrical tests, stimulation with very mild faradic and galvanic currents yielded entirely normal responses in all of the facial and masticatory muscles.

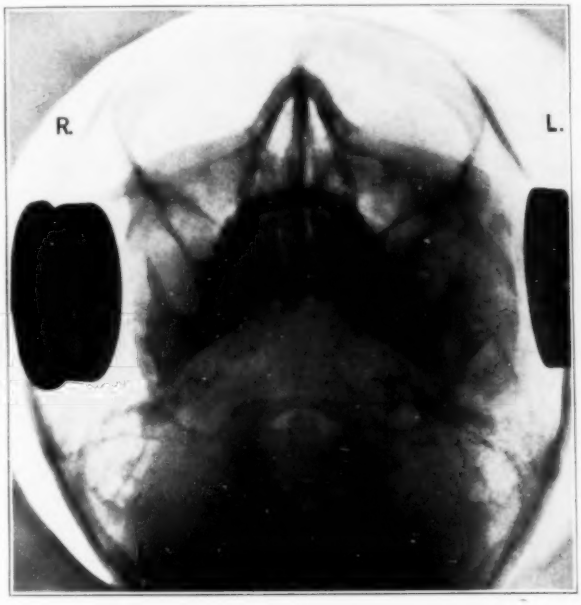

Fig. 2 (case 1).—Roentgenogram taken from above downward, showing mandibular atrophy described in the text.

The teeth were normal, and there was no apparent difference in the width of the alveolar margin between the two sides. The tongue was normally protruded and moved in all directions, and did not participate in the atrophy. Although, clinically, bone atrophy appeared definite in the temporal region and mandible, roentgenograms were rather disappointing. Nevertheless, "a film taken from above downward (fig. 2) shows that the mandible on the right side is closer to the midline than on the left and the ramus appears to be narrower from before backward" (Dr. William P. Howard). Moreover, facial measurements left no doubt as to the participation of the bony structures in the atrophic process. A line drawn from the middle of the chin to the angle of the jaw measured 9 cm. on the right and 10 cm. on the left; a line passing from the root of the nose to the external auditory meatus measured 12.5 cm. on the right and 14 cm. on the left. Careful exploration of the cochlear and vestibular divisions of the eighth

nerve showed perfectly normal reactions on both sides. As regards vasomotor and secretory functions, certain tests only could be carried out. No appreciable difference was detected in the surface temperature between the two sides of the face. When the patient blushed, the phenomenon appeared to be somewhat more pronounced on the right side. In testing the secretory function of the right and left parotid glands, it was definitely ascertained that the left parotid elaborated about 25 per cent more secretion than the right. This difference, however, probably may be explained just as easily by the reduction in bulk of the right parotid as by a presumed reduction of its secretory activity resulting from disturbed vegetative innervation. Particularly interesting are the oculopupillary findings, carefully checked up by the attending ophthalmologist (Dr. Harry V. Judge), who reported as follows: "With the eyes in the primary position, the left eye is on a higher plane than the right. The lower pole of the cornea of the right eye touches the lower lid whereas on the left side the two structures are separated by about 3 mm. of exposed sclera. With a Maddox rod there is no hyperphoria. The corneas are clear with ordinary daylight. The pupil of the right eye measures 4 mm.; that of the left, about 3.5 mm. The right pupil does not react to light either directly or consensually; the left does. In a darkened room the right pupil measures 3.5 mm.; the left, 5 mm. The media of each eye are clear. The disk outlines are sharp and there are no fundus lesions. The retinoscope showed a hyperopic refraction. There is an apparent recession of her near-point on the right side when accommodation is tested, and no contraction of the right pupil on convergence is observed. The visual fields are normal for both form and color." Ocular excursion was full in all directions. A diligent search failed to reveal any focal atrophies or sclerodermal lesions anywhere on the trunk or extremities. Tests of the spinal fluid, including the Wassermann test, gave entirely negative results; the same was true of the blood. The blood picture, chemical composition of the blood and urine and basal metabolism were entirely normal.

Course.—There is little to state beyond the fact that since the patient first came under observation, fifteen months before this paper was written, there has been no perceptible change in the condition.

Comment.—A girl, at the age of 17, received a blow over the right cheek and two weeks later noticed a beginning wasting of the tissues of this part of the face, which increased fairly rapidly and extended to the parotid and submaxillary region as well as toward the temple. The atrophy involved both the superficial and deeper structures in the affected region, and moreover was not confined to the trigeminal distribution, but clearly invaded the domain of the second and third cervical roots according to the dependable schemas of Dejerine.[43] After progressing for two years, the atrophic process apparently came to a standstill. Neuralgic pains in the face were never complained of, and no trace of scleroderma was detected anywhere. Among the many infectious episodes, the triad of tonsillitis, arthritis and chorea occupied a prominent place. A noteworthy feature was the presence of a non-

43. Dejerine, J.: Sémiologie des affections du système nerveux, Paris, Masson & Cie, 1914, vol. 2, p. 831.

syphilitic reactionless pupil on the same side as the hemiatrophy. The paradoxical behavior of the affected pupil in the dark room is likewise interesting. The occurrence of an Argyll Robertson pupil in connection with hemiatrophy has been reported by Oppenheim, Langelaan [44] and Noica and Vicol (mentioned by Wartenberg). Wartenberg interpreted the phenomenon as a spastic mydriasis. In Langelaan's case, however, the pupillary anomaly was on the right side, whereas the facial hemiatrophy was on the left. Moreover, the affected pupil was dilated, and although it reacted to convergence, this reaction was definitely weaker than on the left side. Finally a slight nystagmus of the right eye was observed on conjugate deviation of the eyeballs to either the right or the left. Obviously, the whole syndrome was due to a central lesion involving some of the vegetative pathways above, and others below, their decussation. Langelaan believed that the responsible lesion affected the central sympathetic pathways in their course through the periependymal gray matter of the sylvian aqueduct and oral portion of the fourth ventricle. Recently, Barré [45] issued a word of caution against the too free mention of a nonsyphilitic Argyll Robertson pupil, claiming that in this form, in contrast with the classic Argyll Robertson pupil, not only is mydriasis almost the rule, but pupillary contraction on convergence is likewise absent or markedly weakened; the pupil is not deformed, and the pupillary reactions sometimes vary from one hour to the next. We are much in sympathy with Barré's views. While this type of pupillary disturbance has been encountered in a number of different conditions, which need not be enumerated here, it is mainly in lesions of the tegmentum of the midbrain that its occurrence has been reported. We do not believe that such a localization can be assumed in our case as no concomitant sign indicating a central lesion is present, and the phenomenon is probably best explained by spasm or irritation of the sympathetic dilator fibers of the iris. The moisture of the right side of the face, the somewhat greater flushing on emotional reaction and the definite scantiness of the lateral segment of the right eyebrow also plead in favor of a disturbance of the cervical sympathetic.

Case 2.—*History.*—D. P., a white boy, aged 10 years, first consulted one of us on March 6, 1930, complaining of left facial paralysis of two years' duration and generalized convulsive seizures for one year. The boy was right-handed, and the parents who accompanied him stated that they as well as their other children were right-handed. There was no familial history of tuberculosis, psychopathy or epilepsy save that the father's maternal uncle suffered from recurring

44. Langelaan: * Sur un cas d'hémiatrophie faciale avec signe d'Argyll-Robertson contralatéral, Rev. neurol. **21**:520 (Nov.) 1913.

45. Barré, in discussion on Claude, Velter and de Martel: Méningite séreuse à localisations multiples, Rev. neurol. **37**:667 (Dec.) 1930.

attacks of unconsciousness during which he sometimes sustained severe bruises or lacerations about the head and face. The boy apparently had escaped the usual diseases of childhood with the exception of measles which he had when only 1 year old. There was no history of facial or cranial trauma, radical teeth extraction or other surgical intervention about the nasopharynx, face or cranium. The presumed left facial paralysis, which turned out to be a classic instance of facial hemiatrophy, had first been noticed by the parents when the boy was 8 years old, and had started in the region of the cheek just lateral to the angle of the mouth. It had steadily increased and spread to adjoining parts, more especially toward the malar prominence. One year after the onset of the wasting of the facial tissues, the boy developed periodic attacks of unconsciousness, not preceded by any definite aura and characterized by initial pallor of the face, rapidly followed by increasing cyanosis, generalized tetanic rigidity with hyperextension of the head and subsequent abortive clonic twitchings in the extremities on both

Fig. 3 (case 2).—*A*, atrophic process involving chiefly the region extending from the malar process to the angle of the mouth. *B*, extension of the process to the zygoma, the upper lip and the vertical segment of the mandible.

sides. This clonic phase, which never was as pronounced as the tonic phase, was sometimes wanting entirely. The spasmodic episode lasted approximately four minutes and was invariably followed by a stupor of from thirty to forty minutes' duration. Apparently the boy had never bitten his tongue during the paroxysms, but the parents were uncertain regarding the occurrence of involuntary micturition. After emerging from the stupor, he exhibited an aggressive and even pugnacious attitude which sometimes lasted for several hours. The seizures, which at first occurred about twice a month, had recently increased in frequency and now recurred every week and sometimes at even shorter intervals. As a rule, the attack came on early in the forenoon. There was no complaint of headache or of pains or paresthesias in the left side of the face.

Examination.—The hemiatrophy was relatively circumscribed and roughly corresponded to the distribution of the second division of the trigeminal trunk. The region of greatest shrinkage extended from the malar prominence to the lateral segment of the upper lip, and the entire cheek was markedly sunken in (fig. 3). The atrophy involved in about equally severe fashion all the structures: skin,

subcutaneous fat and connective tissue, muscles and bone. The skin was thinned, smooth and decidedly blanched, particularly over the upper lip and at the angle of the mouth, but was neither shiny, inelastic nor adherent to the underlying structures, and exhibited none of the characteristics of a sclerodermal lesion. When the patient smiled or elevated the upper lip in order to expose the teeth, the skin of this entire region was thrown into numerous fine furrows. The subcutaneous fat had entirely disappeared, and, even clinically, a marked atrophy of

Fig. 4 (case 2).—Roentgenogram showing narrowing of the mandible in both of its segments and other details described in the text.

the malar process was easily ascertainable. The zygoma, mandible and outer wall of the orbit also seemed to be reduced in volume when compared with the homologous structures on the right. By means of ordinary transillumination in a darkened room, the maxillary sinus on the affected side appeared about one-half the size of its fellow, whereas no appreciable difference existed between the two frontal sinuses. This purely clinical impression was immediately confirmed by the roentgen report (Dr. William P. Howard), which read as follows: "The sutures and vascular markings of the skull are normal. The sella turcica is

normal in size and shape. The malar bone on the left side (fig. 4) is not as prominent as on the right. The zygomatic arch is flatter on the left, the mandible is narrower both in the body and in the ramus, and the distance from the midline of the mandible to the angle of the jaw measures less on the left side than on the right." There was no objective sensory loss anywhere in the distribution of the left trigeminal nerve, but pressure over the infra-orbital notch was distinctly more painful on the left than on the right side. The various clinical tests designed to explore the functional integrity of the masticatory muscles (voluntary movements on command and movements against resistance applied by the examiner) revealed no difference between the two sides. The same was true of all the muscles innervated by the facial nerve. Neither group was tested on this occasion with electrical currents. The tongue was protruded normally, executed full excursions in all directions and exhibited neither fibrillation nor atrophy. The soft palate was perfectly intact and elevated symmetrically on phonation without deviation of the uvula. The alveolar margins did not seem to participate in the atrophy, and all the teeth were present and in excellent condition. The musculature supplied by the spinal accessory nerve exhibited neither atrophy nor impaired vigor. Enlarged lymph glands were palpable along both the anterior and posterior borders of the sternocleidomastoid muscle on both sides of the neck, but seemed larger and more numerous on the left side. There was no demonstrable abnormality of the larynx, but the thyroid region was rather full, although clinical signs of hyperthyroidism were totally wanting. Ocular excursion was full in all directions; the pupils appeared equal in size, reacted promptly both to light and in accommodation efforts, and the eyegrounds were entirely normal. There was no difference between the two sides as regards the hair of the scalp, eyebrows and eyelashes. The somatic musculature of the trunk and extremities, the tendon and cutaneous reflexes and the thoracic and abdominal viscera appeared entirely normal as far as could be judged from the clinical standpoint. A searching inspection of the integument of the entire body failed to reveal anywhere the slightest trace of pigmentary anomalies, scars or sclerodermal patches.

Course.—The parents were instructed to limit the patient's fluid intake to less than 20 ounces (591 cc.) a day, and in addition he was given small doses of bromide and phenobarbital. Between March 6 and July 15, 1930, he had two mild attacks in which he merely lost consciousness, exhibited a generalized tonic rigidity of less than two minutes' duration and then remained dazed for a few minutes. The clinical observations at this time were not materially altered. The importance of the dehydration method was again emphasized, but it is known that the patient frequently was insubordinate and had his own way. He was seen repeatedly thereafter, a steadily increasing atrophy of the left side of the face was undeniable, and on Feb. 17, 1931, a complete reexamination was performed. Despite the probably frequent infractions of the dietary regimen, the patient had had only four additional seizures of the mild type previously described.

Reexamination (Feb. 17, 1931).—The aggravation and extension of the atrophy were striking. The wasting of the bony structures of the cheek was so marked that a malar process actually did not exist and the entire region of the cheek appeared as an excavation. The zygoma, the margin of both segments of the mandible and the outer wall of the orbit likewise had dwindled. Transillumination of the maxillary sinus barely revealed its existence on the left side, while there was still no apparent difference between the frontal sinuses. The left eye lay definitely more deeply within the orbital cavity than the right, and the left

pupil was appreciably more dilated (left, 4.5 mm.; right, 3.5 mm.). The nose was deflected to the left and the upper lip was shorter and thinner in its left half. Electrical stimulation of the facial and masticatory muscles with the faradic current revealed not only that all of the muscles without exception yielded excellent responses but that the musculature of the left side of the face showed a decidedly increased excitability, requiring less than one-half the current strength necessary to elicit mild contractions on the unaffected side. Moreover, the patient claimed that the tests were actually painful on the left side.

As regards the cervical sympathetic, the only oculopupillary component present was the dilated pupil on the left side. Its reactions to light and in accommodation and convergence were prompt, but the anisocoria did not disappear during the tests. The various methods elaborately described by André-Thomas [46] to elicit the encephalic pilomotor reflex (trigeminal and upper cervical root domain), such as vigorous pinching of the neck, faradization of the cervicothoracic region, tickling of the axilla and application of ice to the axillary region or to the upper part of the spine, failed to produce any definite response, presumably by reason of our inadequate experience with this important test. Being told by the parents that under emotional circumstances the left side of the face remained more pallid than the right and that in the summer when the patient returned home in a sweat, after playing various games with other boys, running or bicycling, little or no perspiration was seen on the left side of the forehead and face, we verified the fact by placing the boy stripped to the waist directly in front of a heat-generating electrical device for fifteen minutes. At the end of this time the left side of the face and neck was pallid and simply moist, whereas the right side was definitely flushed and freely perspiring. The injection of pilocarpine hydrochloride, 0.01 Gm. (approximately one-sixth grain), produced a similar though less pronounced sudoral reaction which persisted fully one-half hour. The roentgen report on the chest simply stated that the lung markings were accentuated and that there was no definite parenchymal evidence of tuberculosis.

Summary and Comment.—A boy, at the age of 8 years, began to present without ascertainable cause a progressive wasting of the structures of the left side of the face. The atrophic process was first noticed in the mesial segment of the cheek just lateral to the angle of the mouth and steadily increased in severity, extending toward the malar process and the outer wall of the orbit as well as toward the angle of the jaw; it is still progressing at the present time. All the tissues were involved (skin, subcutaneous fat and connective tissue, muscle and bone), but nowhere did the skin exhibit changes characteristic of scleroderma. There were neither subjective nor objective manifestations of involvement of the trigeminal nerve. On the contrary, signs of a disturbance of the cervical sympathetic on the affected side were not wanting, as evidenced by the widened pupil, the pallor of the skin, the relative anhidrosis and the response to pilocarpine. Cervical adenopathies, present on both sides, were more pronounced on the side

46. André-Thomas: Les moyens d'exploration du système sympathique et leur valeur dans les affections organiques du système nerveux, Rev. neurol. **33**:767 (June) 1926.

of the hemiatrophy, but roentgenograms did not reveal definite changes regarded as diagnostic of pulmonary tuberculosis, nor did the tonsils appear infected. About one year after the onset of the facial atrophy, the boy developed generalized convulsive seizures which yielded in an appreciable manner to appropriate therapeutic measures. It is difficult to escape the conviction that, in this case, the facial hemiatrophy resulted from involvement of the cervical sympathetic.

CASE 3.—*History.*—M. H., a white man, aged 24, an electrician, consulted one of us for facial asymmetry on Nov. 20, 1930. He was right-handed, as were all the immediate members of his family. The family history was unimportant as regards epilepsy and psychopathies. The paternal greatgrandmother and her two sisters

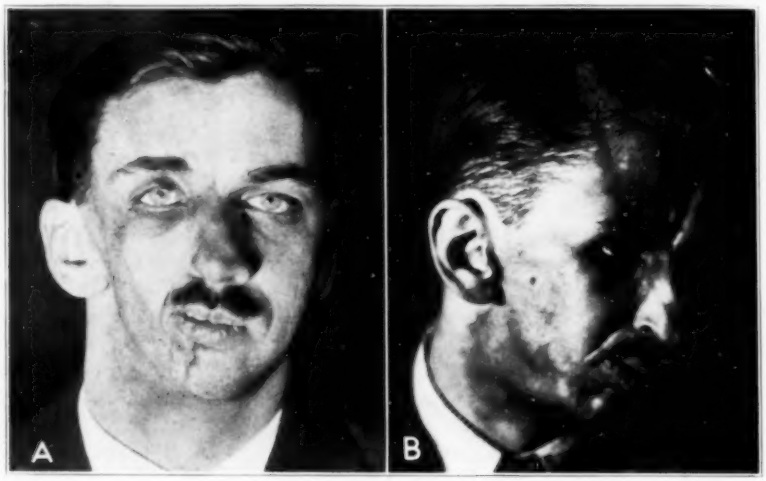

Fig. 5 (case 3).—*A,* extreme and generalized facial hemiatrophy; a definite line of cleavage and pigmented areas over the forehead and the mandibulocervical region. *B,* this picture is intended to bring out the bandlike zone of alopecia, the cleft in the midline of the forehead and the more easily recognizable pigmentation on the affected side.

had pulmonary tuberculosis. Aside from some of the usual diseases of early childhood, there was no evidence that the facial hemiatrophy was preceded by any acute infectious disease, facial or cranial traumatism, extraction of teeth or other surgical operations about the nasopharynx, face or neck. However, the mother stated that labor was prolonged and extremely difficult, forceps being used. On the day following delivery a small black and blue spot, about one-half inch (1.2 cm.) in diameter, appeared below and behind the right ear and lasted a few days.

The facial wasting had its onset when the patient was 9 years of age, and appeared first along the inferior border of the right mandible and in the submaxillary region (second and third cervical root zones). The atrophy had slowly but steadily increased until the entire right side of the face was involved, but there had been no significant change in the condition in the course of the last four years. At no time did the patient experience pains of any kind or paresthesias in the

affected region. An interesting feature is that approximately one year prior to the onset of the facial hemiatrophy the patient began to lose the hair on the corresponding side of the scalp. This alopecia started at the hair line of the forehead and gradually extended in ribbon-like form to the back of the head.

Examination.—The facial hemiatrophy was so striking and generalized that the two sides of the face gave the impression of belonging to different persons (figs. 5 and 6). The dividing line, actually represented by a cleft, if not strictly in the midline, was so close to it that the distinction was purely academic. It was easily recognizable throughout the forehead and over the greater portion of the nose

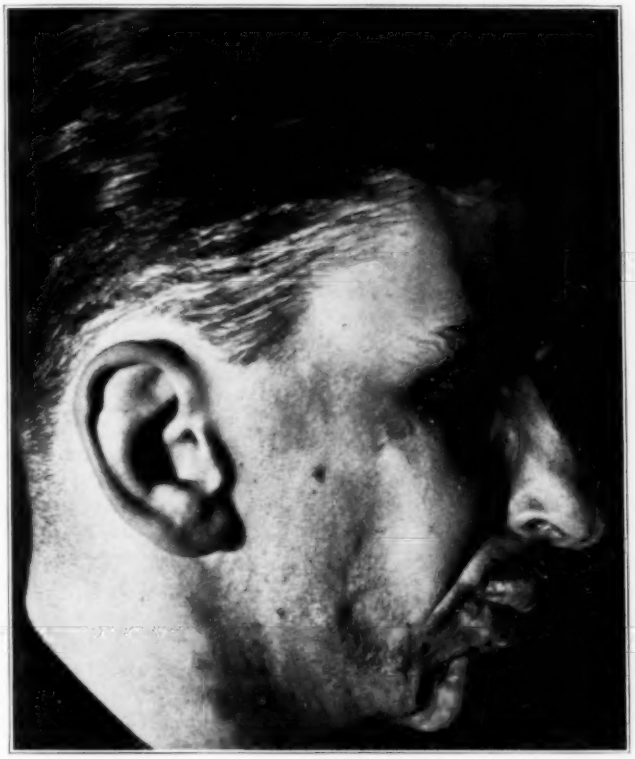

Fig. 6 (case 3).—Picture showing the deep groove over the forehead, the bifid nasal cartilage and the marked wasting of the entire mandibular area.

as well as over the lower lip and the chin, and only at the point of the latter was the line of cleavage deflected to the right. The most pronounced areas of atrophy involved the lower half of the forehead, the inner half of the supra-orbital ridge, the temporal region, the lateral segment of the malar process and the whole of the mandibular region. In addition, the posterior frontal and the entire parietal region was the seat of a broad shallow depression occupied by a sharply delimited bandlike zone of alopecia, measuring approximately 10 cm. in length and 2.5 cm. in width, that extended all the way from the hair line of the forehead to a point about midway between the coronal and lambdoid sutures (the domain figured by Dejerine as the common innervation zone of the trigeminal nerve and second

cervical root). In this region, as well as over the entire right side of the face and neck, the skin was thinned, moist, perfectly smooth, freely movable and at no point adherent to the subjacent structures. It did present, however, a diffuse and striking hyperchromia, most pronounced in the mandibular and cervical regions where the extensive plaque had a dark brownish-yellow color. On the forehead, where the color was less deep, the area of pigmentation had a somewhat rhomboid outline and occupied the inner two thirds of the forehead, being limited mesially by the midline and laterally by an oblique line running from the middle of the supra-orbital ridge to the hair line. In its greatest width at the hair line it measured 6.5 cm., and at the supra-orbital margin 4 cm. The right eye was sunken and occupied a definitely lower plane than the left.

The atrophic process involved not only the skin but likewise the subcutaneous fat, connective tissue, muscle, cartilage and bone. The nasal cartilage was so definitely reduced in size in its right half that the tip of the nose was actually bifid and deflected to the right. The ear did not participate in the atrophy nor did the mastoid process. The subcutaneous fat was wanting throughout the affected side of the face, save in the region of the malar eminence. The upper and lower lips were both shorter and thinner on the right side. The atrophy of the superior maxilla and mandible was striking and the superior alveolar process appeared to be definitely narrower on the right side. The patient has a narrow high palate, but the soft palate, tongue and larynx apparently were intact. Ordinary transillumination showed a decided difference between the right and left frontal and maxillary sinuses. The roentgen report (Dr. William P. Howard) gave the following information: "The sutures and vascular markings of the skull are normal. The right frontal and parietal bones are definitely thinner than the corresponding bones on the left side of the skull. The right superior maxilla, malar process and mandible are smaller than the corresponding bones on the opposite side (fig. 7). The ramus is shorter, causing the face to assume a twisted attitude with the convexity toward the left. The mastoid process and the extent of the cells is the same on the right side as on the left." The beard on the right side was very scanty, and according to the patient's statement was only one fourth as abundant as on the left. The eyebrow throughout was less developed on the right side, the difference being especially striking in the lateral segment. Superficial and deep sensation throughout the right trigeminal fields was intact, but the right supra-orbital nerve was slightly more sensitive to pressure than the left. The masticatory and facial muscles exhibited normal function and strength, so far as could be determined from active movements and movements effected against resistance. Ocular excursion was full in all directions; both pupils reacted very actively to light and in accommodation efforts but, whereas the left pupil remained contracted under sustained illumination, the right one definitely rebounded. The eyegrounds were entirely normal. There was no atrophy of the trunk or limbs on either side, nor could the slightest evidence of scleroderma be detected anywhere. Physical and roentgenographic studies failed to reveal the presence of recent or old apical pulmonary tuberculosis.

On a subsequent occasion (Dec. 13, 1930) an effort was made to explore in detail the functions of the cervical sympathetic. Oculopupillary abnormalities were entirely wanting save for the tendency of the right pupil to rebound under sustained illumination. As in case *2*, the tests of André-Thomas for the encephalic pilomotor reflex were repeatedly and vigorously applied, but we were unable to elicit any response on either side of the face and neck, whereas a definite reaction

appeared on the upper part of the chest.[47] The vasomotor reflex proved more interesting. The application of a galvanic current of from 8 to 10 ma. over the cheek during a period of four minutes produced a definite rounded zone of hyperemia which persisted on the right side of the face for several minutes, while no appreciable flush was observed on the left side. Exposure of the face, neck and chest to a heat-radiating apparatus during a period of approximately ten minutes provoked a decided flush of the exposed skin which seemed deeper and more

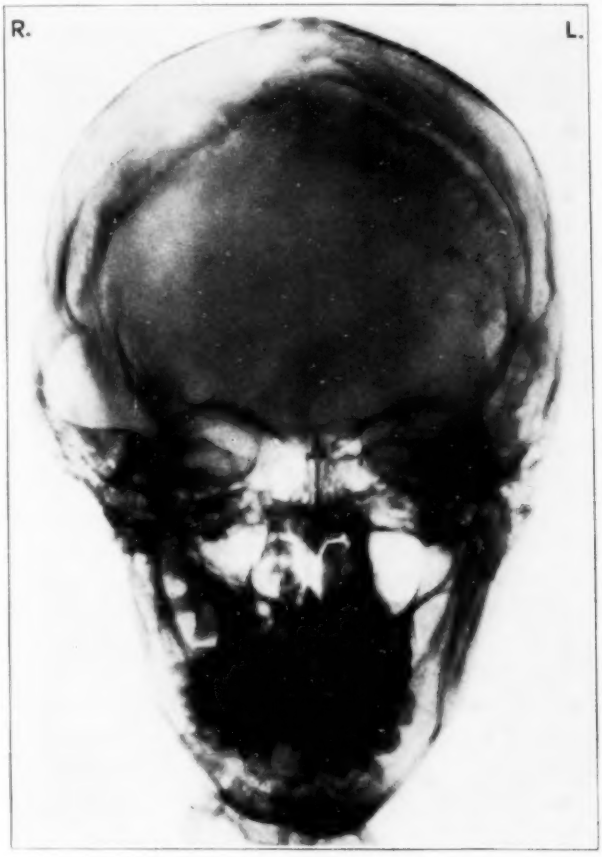

Fig. 7 (case 3).—Roentgenogram showing the crude asymmetry of the bony structures and other features described in the text.

extensive on the right side of the face and thorax despite the presence of the two large areas of hyperchromia on the forehead and over the anterior triangle of the neck which naturally would interfere with accurate observation. This test, primarily designed to objectivate any material difference in the sudoral activity of the two sides of the face and neck, actually determined no sweating whatever, possibly by reason of an insufficient degree of heat. Electrical stimulation revealed

47. It has been admitted by André-Thomas himself that the encephalic pilomotor reflex is particularly difficult to objectivate.

in this case, as in case 2, a decided increase of electrical excitability of the nerves and muscle (facial and masticatory) of the affected side. A current, of such mild intensity that no response whatever could be elicited on the left side of the face, produced on the right side extremely vigorous contractions of all the muscles. In addition, these tests were so disagreeable and even painful to the patient that he complained of the discomfort and instinctively drew the head away. This increase of electrical excitability was much more pronounced than in case 2.

Course.—The patient was seen and reexamined on several occasions between Nov. 20, 1930, and April 6, 1931, and not the slightest evidence of aggravation was detected.

Summary and Comment.—A man, aged 24, presented a right craniofacial hemiatrophy which first became apparent at the age of 9 and was preceded by a circumscribed alopecia on the corresponding side of the head. No immediately antecedent cause was discovered, but it is known that labor was extremely difficult, necessitating the use of forceps, and that after birth the right side of the neck was the seat of an ecchymosis which disappeared within a few days. While much reliance cannot be placed on a mother's memory of so remote an event and particularly on her description of the extent and severity of the cervical abnormality, it is believed that the possibility of a deeper contusion than one would associate with a simple ecchymosis cannot be dismissed entirely.

Of our 3 cases this was the most severe and extensive. All the structures of the affected side of the face and cranium were involved, practically to the same degree. There are three features that compel a comparison with Wartenberg's case. In both, the facial hemiatrophy was preceded by a bandlike zone of alopecia starting at the forehead and gradually extending to the posterior parietal region. In Wartenberg's case the beard was much more abundant on the affected side, whereas in our case the reverse was true. In both instances the masticatory and facial musculature exhibited increased electrical excitability. Wartenberg correctly interpreted the latter phenomenon as due to the disappearance of the subcutaneous fat and connective tissue and the consequently more direct accessibility of the nerves and muscles. He likewise commented on the fact that, contrary to the view held by Oppenheim and by Curschmann, the hair of the scalp does not invariably escape. Mention also should be made of the analogies existing between Klingmann's [40] case, to be summarized presently, and our own. In our patient there were no signs, subjective or objective, of involvement of the trigeminal nerve. On the other hand, evidences of sympathetic dysfunction were numerous and prominent. The extensive pigmentation, the alopecia, the hypotrichosis of the face, the definitely greater hyperemia (galvanism, heat) over the right side of the face, neck, and chest, revealing a distinct vasomotor asymmetry, and perhaps the

rebounding pupil on the right side leave little room for doubt. Moreover, it is to be noted that all of our patient's anomalies lay within the territory innervated by the postganglionic fibers derived from the superior cervical sympathetic ganglion (trigeminal and upper four cervical root zones) as André-Thomas well established.

ETIOLOGY AND CLINICAL ASSOCIATIONS

I. The influence of hereditary factors in the genesis of facial hemiatrophy and the familial incidence of this condition were considered negligible by Marburg, who mentioned only the cases of Raymond and Sicard [28] which concerned two sisters, aged 17 and 18 years, respectively, who developed an ascending hemiatrophy beginning in the lower extremity, and the case of Klingmann [40] about which his meager statement is misleading. Owing to its great interest, Klingmann's case deserves a brief description.

The patient, a girl, aged 16, developed a right facial atrophy when 7 years old. One of the first manifestations noted by the mother was the falling out of the hair just to the right of the midline. At the time of examination, a linear zone of alopecia, about 2 cm. in width, extended from the forehead upward and backward over the vertex and occupied throughout an immediately parasagittal position. The bone in the corresponding region exhibited a deep groove and the forehead was the seat of a fairly circumscribed pigmented area. (All three of these features are common to Klingmann's case and our case 3.) The patient's little finger on both sides was crooked and abnormally short. Her twin sister had a definite facial asymmetry (the careful measurements fully specified by Klingmann being less on the right side). Finally, this twin sister, a brother, the mother and the grandmother all presented the anomalies of the little fingers noted in the patient.

Wartenberg was much more emphatic about the significance of hereditary and familial factors, and to the preceding cases he added the observations of Boenheim [48] (case 2), Reiss [49] and Geist.[50] Boenheim's case was an instance of congenital facial hemiatrophy, and the only additional point of interest was that the patient's sister had a facial asymmetry with deviation of the mouth to one side. In the case reported by Reiss, the patient herself had a left facial hemiatrophy; the mother presented a definite facial asymmetry, the right side being smaller than the left (no measurements are given), and the patient, her mother and maternal grandmother all suffered from migraine. When one realizes how common facial asymmetry actually is, the foregoing evidence in favor of a hereditary factor in the genesis of facial

48. Boenheim: * Zur Pathogenese der Hemiatrophia faciei progressiva, Deutsche Ztschr. f. Nervenh. **65**:219, 1920.

49. Reiss: * München. med. Wchnschr. **63**:1331, 1916.

50. This author was mentioned by Wartenberg in connection with total hemiatrophy. We have not succeeded in locating his publication.

hemiatrophy does not seem to us to possess much significance. By far the most valid case is Klingmann's.

Moreover, Wartenberg called attention to the fact that congenital defects are not particularly rare in cases of facial hemiatrophy, such as congenital facial palsy, congenital ocular palsies and congenital lingual hemiatrophy; he mentioned the cases of Ellerbroeck, Emerson and Harbitz. A few more such instances are to be found in the literature. We already have referred to Norman Tobias'[33] case with a right congenital ptosis and a left congenital total hemiatrophy combined with an extensive nevus of the left side of the cranium and face, as well as to the occurrence of 3 or 4 cases of congenital facial hemiatrophy. It is our belief that the list of all such cases is not impressive enough to have real etiologic significance. It may be noted, in addition, that in some of these cases there was a history of birth trauma. This was specifically mentioned in the case of Huber[51] and in the thesis of Tournaire.[52]

H. Oppenheim mentioned as a possible etiologic factor the previous occurrence of an infectious disease, such as diphtheria, erysipelas, typhus fever, measles, scarlet fever, etc., but, as Marburg correctly stated, the rôle of infectious diseases is difficult correctly to evaluate as a long interval frequently elapsed before the onset of the facial hemiatrophy. To our mind what renders the problem particularly difficult is the fact that the condition develops predominantly during childhood and adolescence, which is precisely the period of life when infectious processes of various kinds are admittedly most common. However, Sterling,[53] a warm advocate of the sympathetic theory, recently reported 4 cases of facial hemiatrophy coming on soon after the evolution of an infectious process.

In his first case, a girl, aged 6 years, following an abscess of the left inferior alveolar region, developed a left facial hemiatrophy accompanied by a Horner's syndrome on the same side. In the second case, a boy, aged 7 years, following diphtheria, presented a left facial hemiatrophy, associated with a homolateral Horner's syndrome and a paresis of the left abducens nerve. The third case concerned a girl, aged 9 years, who after recovering from the acute stage of epidemic encephalitis developed a left facial hemiatrophy combined with Horner's syndrome, excessive sweating, salivation, rhinorrhea and hypothermia, all on the same side of the face. In the fourth case, that of a boy, aged 11 years, entering the chronic stage of the usual spinal form of poliomyelitis, most of the teeth fell out and a bilateral facial atrophy developed.

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51. Huber: * Hemiatrophia facialis progressiva, Arch. Pediat. **16**:2 (Feb.) 1899.

52. Tournaire: * De l'hémiatrophie faciale dans les paralysies du plexus brachial, Thèse de Lyons, 1904.

53. Sterling: Hémiatrophie faciale d'origine infectieuse, Rev. neurol. **34**:138 (July) 1927.

The central origin of Sterling's third and fourth cases is obvious and it is probable in his second case. The important feature is the presence of an oculopupillary syndrome in 3 of the 4 cases. In addition to Sterling's third case, facial hemiatrophy following encephalitis, whether of epidemic or other type, was recorded by Wartenberg,[6] Mankowski [24] and E. Kirschenberg [54] and seems probable in H. G. Wolff's [23] case.

Far more important, however, among infectious processes, is pulmonary tuberculosis by reason both of the common apical pleuritis and the cervical adenopathies. Strongly emphasized by the earlier writers (Bouveyron, Barrel, Jaquet, Oppenheim and others), the significance of this factor does not seem to have retained sufficiently the attention of recent authors. Although listed in Wartenberg's bibliography, the important contributions on this relationship by Siebert,[55] by Weinberg and Hirsch [56] and by Loewy-Hattendorf [57] are totally ignored in the text despite the fact that each of the last two references applies to 4 cases. In one of L. Cerni's [58] cases, that of a patient with apical tuberculosis and obvious pleuritic and peripleuritic adhesions, a deep scar in the lower cervical region involved skin and muscles and practically extended to the corresponding vertebrae. On the same side there developed a facial hemiatrophy accompanied by Horner's syndrome. In our case 2, although pulmonary tuberculosis was not demonstrable either clinically or by means of roentgen rays, the cervical lymph glands were distinctly enlarged, more so on the side of the hemiatrophy.

III. Möbius, Oppenheim and Marburg mentioned the not uncommon development of facial hemiatrophy in connection with local infectious processes (angina, alveolar abscess, tonsillitis, periostitis or osteomyelitis of the lower jaw, etc.); likewise following extirpation of adenoids and extraction of teeth. Marburg mentioned fully six authors in whose cases the atrophic process appeared after the extraction of teeth, and stated that in such cases the condition may develop rapidly. A pertinent example is the recently reported case of Bönheim.[59]

54. Kirschenberg, E.: Zur Frage der Hemiatrophia faciei progressiva mit zentraler Genese, Folia neuropath. estoniana **5**:94 (March) 1926.

55. Siebert: * Ein Fall von rechtseitigen Gesichtsmissbildung mit Erscheinungen der Hemiatrophia faciei, Deutsche Ztschr. f. Nervenh. **56**:320, 1917.

56. Weinberg and Hirsch: * Hemiatrophia facialis progressiva bei chronischen Lungenaffektionen, Deutsche Ztschr. f. Nervenh. **66**:204, 1920.

57. Loewy-Hattendorf: * Lungentuberculose und Hemiatrophia faciei, Zentralbl f. d. ges Neurol. u. Psychiat. **27**:413, 1921.

58. Cerni, L.: Zur Frage der Klinik und Pathogenese der Hemiatrophia faciei, Ukrain. med. visti, 1925, vol. 63, nos. 5 and 6; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **43**:693, 1926.

59. Bönheim, E.: Zahnextraction, periphere Facialislähmung, Hemiatrophia facialis progressiva, Deutsche Monatschr. f. Zahnh. **45**:353, 1927.

A girl, aged 13 years, had a right upper molar extracted and this was followed immediately by right facial weakness and hypesthesia of the right side of the face, as well as by the appearance of a dark pigmented area in the nasolabial fold and a whitish streak on the upper lip on the same side. These various manifestations cleared up entirely in the course of a few weeks, but at the same time signs of a right facial hemiatrophy began to be manifest and subsequently increased with maximum intensity about the cheek and malar region. The right palpebral fissure was definitely wider than the left.

A case reported by H. Krueger [19] is equally interesting though more complicated.

The patient, when 22 years of age, following the extraction of an upper left molar, which was attended with severe hemorrhage, soon noticed the progressive sinking in of the tissues over the corresponding superior maxilla. In addition, he gave a history of receiving a severe blow on the left side of the face while attending school a few years before. The wasting progressed relatively slowly until he sustained an injury to the left side of the forehead and head as the result of a railway accident. Following the latter trauma, the atrophy evolved much more rapidly and extended to the frontal region. The patient never experienced any pain on the affected side and presented neither pigmentation, thermal asymmetry nor oculopupillary phenomena. The bone definitely participated in the atrophic process and the left eyebrow was decidedly sparser than the right. This case is likewise of importance by reason of the fact that objective sensory losses were present in all three divisions of the corresponding trigeminal nerve and that the patient exhibited tonicoclonic spasms of the masticatory musculature, the duration of which varied from fifteen seconds to one minute and seemed incited particularly by exposure to cold. The author believed that a lesion of the pons involving the trigeminal nuclei or their immediate proximity was responsible for the clinical manifestations.

Closely analogous to Krueger's case is that reported by Bernard Sachs,[60] although neither extraction of teeth nor craniofacial traumatism antedated the onset of the facial atrophy.

The patient, a woman, presented a left facial hemiatrophy which had its onset at the age of 18. Clonic and tonic contractions of the temporal and masseter muscles, which sometimes extended to the tongue, occurred at intervals and were brought on apparently by excitement or by exposure to cold. There was an associated lingual hemiatrophy but no evidence of scleroderma. Pain sense was faintly diminished over the left side of the face. The electrical reactions of the facial and masticatory musculature were entirely normal. Thermometric measurements of the external ear consistently showed a difference of 1 degree in favor of the right ear.

IV. Traumatism, particularly about the cranium, face or neck, as a common antecedent in case histories of facial hemiatrophy has been

60. Sachs, Bernard: * Progressive Facial Hemiatrophy with Some Unusual Symptoms, M. Rec. **37**:292, 1890

stressed in the older literature by Seeligmüller, Stepp,[61] Tournaire,[52] Minor, Huber,[51] Oppenheim, Otto Kracht,[62] Cassirer and Marburg, and more recently a history of severe traumatism was given in the cases of Dejerine and Krebs,[63] Krueger,[19] Souques and Bourguignon,[42] Stiefler,[17] Stief, Sándor and Tanka,[10] Trabaud,[64] Popova,[32] Trömmer,[65] Boguslawski,[18] Sterling[38] and Crawford Bost.[66] It was definite in our case 1 and suggested in our case 3. The incidence of previous injury has been estimated at anywhere from 24 to 34 per cent by different authors. Although in some cases years have elapsed between the injury and the onset of the atrophy, in the great majority the interval has been short, from two or three weeks to a few months. This fact, coupled with the development of wasting on the same side of the face and its initial appearance at the very seat of injury, is too impressive and the number of such cases too considerable to be ignored. Marburg and Wartenberg both maintained that traumatism does not represent the fundamental cause of the facial hemiatrophy, but simply exerts a localizing influence. We are not so sure that this interpretation is correct. Whether or not separate trophic nerve fibers exist, as Samuel originally believed, or whether such fibers course or are identical with the vasomotor nerves, as was taught by Stilling and by Bergsohn, is a question that thus far has not been settled definitely and to which we shall return in a subsequent section. Assuming that they do run in the perivascular sheaths, it seems entirely logical to believe that a local injury would of itself be competent to initiate a trophic disturbance, as it is almost universally conceded that the primary and outstanding effect of traumatism exerts itself on the blood vessels of the region involved, though frequently reaching the vasculature of more deeply or remotely situated structures.

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61. Stepp: * Beitrag zur Beurteilung der nachheftigen Körpererschütterungen (bei Eisenbahnunfällen) auftretenden Störungen, Deutsche med. Wchnschr. **15**:66, 1889.

62. Kracht, Otto: * Ueber Hemiatrophia faciei progressiva, Inaug. Dissert., Jena, 1905.

63. Dejerine, J., and Krebs, E.: Paralysie radiculaire du plexus brachial d'origine traumatique et datant de l'enfance avec syndrome sympathique. Hémiatrophie faciale et troubles sensitifs étendus, Rev. neurol. **22**:321 (Feb.) 1914.

64. Trabaud: Blessure carotidienne droite. Syndrome médullo-sympathique caractérisé par une hémiatrophie faciale gauche et des troubles vasculaires du membre supérieur du même côté. Mydriase gauche paradoxale, Rev. neurol. **34**:244 (Feb.) 1927.

65. Trömmer: Hemihypertrophia und Hemiatrophia faciei, Deutsche med. Wchnschr. **53**:820, 1927.

66. Bost, Crawford: Progressive Facial Hemiatrophy: Report of a Case in a Child, Arch. Pediat. **44**:497, 1927.

V. The various clinical associations of facial hemiatrophy have been particuluarly emphasized by Oppenheim. Its close relationship to scleroderma has been stressed almost from the start and, by reason of its important bearing on the problem of pathogenesis, will be discussed later under that heading. The occurrence of neuralgia of the face has already been mentioned, as well as the fact that Oppenheim considered it an extremely important prodromal symptom. Psychoses are not uncommonly mentioned, particularly in connection with cases developing late in life and in symptomatic forms encountered in patients suffering from extensive cerebral degeneration. Similarly, a marked mental defect has been observed, especially in the total hemiatrophies of congenital origin.

Chorea is occasionally recorded in the patient's previous history, but not frequently enough to deserve more than passing mention. In our case 1, the patient had an attack of chorea about ten years prior to the onset of the atrophy. Admitting a possible relationship, one would be justified only in grouping chorea with other systemic infections already mentioned.

The occurrence of epilepsy, whether of the so-called idiopathic and generalized form or of the jacksonian type, is more interesting. Wartenberg, whose patient exhibited both, although the seizures were predominantly jacksonian, unequivocally expressed the opinion that there is more than pure coincidence between the two, and erected a most elaborate hypothesis to affirm his position. We regret that we cannot here furnish the full detail of his theory, but the essential feature is that facial hemiatrophy, the primary clinical manifestation, would result from a lesion of the higher vegetative centers in the diencephalic floor, that sympathetic innervation disturbances would soon affect the vasculature of the homologous cerebral hemisphere and thus predispose this hemisphere to subsequent toxic or infectious invasions, which would account for the occurrence of jacksonian seizures in the contralateral extremities. Up to 1925, Wartenberg had collected only 4 cases of generalized and 4 cases (including his own) of jacksonian epilepsy. Since that date we have found 3 additional cases, those of Lauber [67] and H. G. Wolff [23] and our case 2, all of them exhibiting generalized seizures. This brings the total number up to 11 and we have no doubt that Wartenberg, like ourselves, has overlooked some cases. Nevertheless, we think that there is nothing astonishing in the fact that, rare as it is, facial hemiatrophy should occasionally appear in a person suffering from so common a disease as epilepsy. The number of such cases, even admitting that our count falls short, is still too insignificant

67. Lauber, H.: Ein Fall von Hemiatrophia facialis progressiva mit Beteiligung des Auges, Ztschr. f. Augenh. **57**:492, 1925.

when one remembers that the total number of cases of facial hemiatrophy thus far recorded probably exceeds 400. Again, it is well to bear in mind that not all cases of so-called jacksonian epilepsy indicate a focal cerebral lesion. The most alluring fact in connection with this problem is that in the majority of the 11 cases referred to, the convulsive episodes appeared some time after the hemiatrophy had become definitely recognizable. In this respect, the literature would substantiate Wartenberg's views.

Migraine, a close relative of epilepsy, has been encountered repeatedly in connection with facial hemiatrophy, and Wartenberg mentioned 6 cases exhibiting this association. It has already been pointed out that Reiss'[49] patient suffered from migraine and the same is true of the case reported by Souques and Bourguignon.[42] Whatever its significance, this association would plead in favor of the sympathetic theory if the conclusions reached by recent investigators on the pathogenesis of migraine mean anything.

The occurrence of tonic or clonic spasms of the facial, masticatory or lingual musculature, stressed by Oppenheim and others, has already been mentioned in the summary description of the cases of Krueger[19] and B. Sachs,[60] and in the recently reported case of Kirschenberg[54] closely analogous manifestations were prominent in the clinical picture.

> The patient, a woman, aged 28, rapidly developed a right facial hemiatrophy in the course of one year following a grippal infection. A tonic spasm of the masticatory muscles determined a frequently recurring trismus. Hyperhidrosis and hypesthesia were present on the right side of the face. The author incriminated a lesion immediately above the trigeminal nuclei.

Cases of this sort presumably all are of central origin and we would interpret the spasm as part and parcel of the syndrome rather than as a clinical association.

Facial paralysis has been observed a few times in cases of facial hemiatrophy. It may antedate the facial atrophy, as in the cases of Kreitmer, Marie and Marinesco (mentioned in Marburg's bibliography), Huber[51] and E. Bönheim,[59] or it may develop coincidently (the case of Léri) or a considerable time after the hemiatrophy has become constituted as in the three cases so well reported by Gowers.[68]

In the latter author's first case the facial paralysis was marked, but was not recognized until several years after the onset of the hemiatrophy. In the second case, likewise, the facial palsy developed definitely at a later date; moreover, it was incomplete and associated with annoying spasms of the musculature innervated by both the upper and the lower branches of the facial nerve. In the third case, the facial

68. Gowers: * The Influence of Facial Hemiatrophy on the Facial and Other Nerves, Rev. Neurol. & Psychiat., Edinburgh **4**:1 (Jan.) 1906.

paralysis was incomplete and associated with weakness of the soft palate and vocal cord as well as with marked impairment of hearing, all on the same side.

Gowers expressed the opinion that the involvement of the cranial nerves could well result from the strangulation of these nerves in their course through the narrowed foramina and canals (aqueductus fallopii, foramen lacerum) located in the temporal bone, itself so commonly a participant in the atrophic process. Attractive as Gowers' hypothesis undoubtedly is, it is well to point out that it can apply only to cases in which facial paralysis develops after the facial hemiatrophy has reached a fairly advanced stage, and by this time the denudation of the facial nerve, throughout its peripheral course from its point of exit at the stylomastoid foramen, renders it particularly vulnerable. Furthermore, another factor may account for the relatively frequent occurrence of atrophy and perhaps slight weakness of the facial, masticatory, palatal and lingual musculature, although as a rule there is no impairment of either function or electrical reaction, as has been emphasized already. If, as we believe, facial hemiatrophy is due in the large majority of cases to involvement of the cervical division of the sympathetic system, one cannot fail to take into consideration the important fact that other cranial nerves besides the trigeminal receive a contingent of sympathetic and parasympathetic fibers. Most anatomists describe sympathetic filaments derived from the carotid and cavernous plexuses which pass to the third, fourth, fifth, sixth and seventh cranial nerves, while the root ganglia of the glossopharyngeal and pneumogastric nerves and the hypoglossal nerve receive direct branches from the superior cervical sympathetic ganglion.

The association of facial hemiatrophy with organic disease of the central nervous system has been observed in multiple sclerosis by Jolly [69] whose patient, it should be stated, presented a bilateral facial atrophy and also suffered from pulmonary tuberculosis. Apparently this is the only case of multiple sclerosis mentioned in the literature of facial hemiatrophy. In tabes dorsalis, Marburg's bibliography listed the case of G. Bassi, and one of us recalls seeing this same association in the service of Professor Raymond at La Salpêtrière, although the case apparently never was reported. Facial hemiatrophy has been observed repeatedly in connection with syringomyelia, but this association has such an important bearing on the question of pathogenesis that it can be discussed more advantageously under that heading.

PATHOLOGIC ANATOMY

Thus far, only 3 cases of so-called idiopathic or essential facial hemiatrophy have been studied anatomically, those of Mendel, Loebl

69. Jolly: * Ueber multiple Hirnsklerose, Arch. f. Psychiat. **3**:711, 1872.

and Wiesel and Erich Grabs. The findings in the first two were so well summarized in Marburg's monograph that we can do no better than transcribe them here:

In Mendel's case a proliferative interstitial neuritis involving all branches of the trigeminal from their gasserian origin to the periphery, but most marked in the second division, was found. In addition, there was an atrophy of the corresponding substantia ferruginea and descending spinal root of the fifth nerve, and the gray matter at the level of the fifth cervical cord segment was somewhat degenerated.

In Loebel and Wiesel's case, a proliferative interstitial neuritis of the peripheral divisions of the trigeminal likewise was present and involved the mandibular and maxillary divisions with equal severity. In addition, proliferative changes in the mesodermal elements and numerical reduction of the ganglion cells and nerve fibers were observed in the gasserian ganglion as well as in the sphenopalatine, otic and ciliary ganglia. No pathologic changes were found central to the gasserian ganglion, and the sympathetic chain was intact. In both of the cases cited severe tuberculosis of the lungs and lymph glands was present.

In the case of Erich Grabs,[70] that of a patient who eventually died of advanced pulmonary tuberculosis, there was a right facial hemiatrophy unaccompanied by subjective pains, objective sensory losses or pigmentation, but a decided falling out of the hair (mustache and beard) on the affected side had been an early manifestation. Histologically, sections of the superior cervical sympathetic ganglion, the gasserian ganglion and its three peripheral divisions and serial sections of the brain stem all the way from the level of the hypoglossal nucleus to that of the oculomotor revealed no demonstrable changes. Professor Rothmann examined the sections and confirmed the absence of pathologic changes.

No mention was made by Grabs of any examination of the pleuropulmonary apexes, the inferior cervical sympathetic ganglion, the perivascular plexus or the cervical cord. It is well known that, except in the hands of the elect and until recent years, staining methods for histologic changes in the sympathetic fiber system were rather unsatisfactory. Grabs' conclusion that facial hemiatrophy may exist in the absence of any discernible changes in either the trigeminal or the sympathetic system is perhaps not entirely justified. One feature surely is important and that is the presence of advanced pulmonary tuberculosis in all 3 cases that thus far have come to necropsy.

70. Grabs, E.: * Ein Fall von Hemiatrophia faciei progressiva, Neurol. Centralbl. **33**:85 (Jan.) 1914.

In the symptomatic group of facial hemiatrophies, Marburg mentioned several cases of syringomyelia (to which we shall refer later), the bulbopontile lesions of various types actually found or surmised in the cases of H. Schlesinger, Marie and Marinesco and Gowers, and the cases of Gräfe and of Solomon in which ocular palsies were present in patients having syphilis. In the tumor group, he referred to the case of Homen (tumor of the middle fossa), to that of Muratow (echinococcus disease of the middle and posterior fossae) and to his own case of cerebellopontile angle tumor, in which he courageously admitted that the trigeminus was intact both clinically and anatomically. Mention was also made of one of Touche's cases in which this author found a focus in the lenticular nucleus and the adjoining segment of the internal capsule and another focus in the midbrain which extended caudally to the region of the trigeminal nuclei. Finally, Marburg recalled the occasional occurrence of verified or presumed hemispheral lesions, encephalitic or otherwise, in cases of total hemiatrophy (Henschen, Raymond and Sicard,[28] Orbison). Marburg, who evidently leaned toward the trigeminal theory without formally saying so, stated that in the majority of so-called symptomatic cases, the lesions (including neoplasms) were so located as to compress or otherwise involve the trigeminal nuclei or their fiber pathways. Apparently he lost sight of the fact that, centrally as well as peripherally, the trigeminal and sympathetic systems are intimate neighbors. Dejerine and Krebs'[63] case of cervical hematomyelia, countless cases of syringomyelia and syringobulbia, the syndrome of occlusion of the posterior inferior cerebellar artery and the various bulbopontile syndromes (syndromes of Avellis and Babinski-Nageotte) bear witness to the correctness of this assertion.

PATHOGENESIS

A great many theories have been advanced to account for this peculiar dystrophy.

Sclerodermal Theory.—Unquestionably the most puzzling problem to elucidate is the relationship of facial hemiatrophy to scleroderma. The first to call attention to this relationship were Bitot and Lande in 1870, soon followed by Eulenburg, Möbius and a host of others. Cassirer,[30] who incorporated facial hemiatrophy in the remarkable chapter that he devoted to scleroderma, both in his original monograph and in his subsequent contribution to Lewandowsky's *Handbuch der Neurologie*, cited no less than fifteen authors from the previous literature who had openly expressed their conviction of the sclerodermal nature of this interesting dystrophy. Universally recognized as the most militant supporter of the sclerodermal theory, Cassirer based his views on the large number of cases in which facial hemiatrophy was

accompanied by scleroderma in other parts of the body and saw no material differences between the two. His teaching had a world-wide repercussion and numerous authors soon rallied to his support. It is well known that not only since but even before Cassirer's time facial hemiatrophy found a much more detailed description in textbooks of dermatology than in those of neurology. In more recent times a large number of articles favoring the sclerodermal nature of facial hemiatrophy have appeared in the literature, namely, those of Verrotti,[71] Kahn and Baruk,[72] O. L. Levin,[73] Osborne,[74] Stief, Sándor and Tanka,[10] L. Cerni (case 2),[21] Petrillo and Oreggia,[75] Boardman,[35] Wolff and Ehrenclou,[76] H. G. Wolff,[77] O'Leary and Nomland,[36] Trepte[15] and J. J. Eller.[34] Cassirer, who incriminated a lesion of the vasomotor contingent of the sympathetic system as responsible for both scleroderma and facial hemiatrophy but denied the possibility of a more exact localization (the sympathetic chain, ganglia and anastomotic junction of the sympathetic and trigeminus, as proposed by Jendrassik), claimed that in both conditions there is a disappearance of subcutaneous fat, atrophy of the skin and adhesion of the latter to the underlying structures and particularly to the bone, achromia or hyperchromia, dilatation of the superficial venous channels, anomalies of hair growth, etc. Many but not all of these assertions are true. If the skin as a rule is involved, there are many instances when it escapes entirely and the fact previously has been brought out that both Marburg and Wartenberg mentioned a large number of authors whose cases illustrated this point. This being so, the term scleroderma, by its very definition, becomes meaningless. As regards adhesion of the atrophied skin to the subjacent muscle or bone, there are few cases in the litera-

71. Verrotti, G.: Di un caso emiatrofia sclerotica del viso a sinistra estesa a tutto territorio della 3ª branca de 5° paio con incipiente diffusione al territorio della 1ª et 2ª branca, Gior. ital. d. mal. ven. e d. pel. **50**:419 (Nov.) 1915.

72. Kahn and Baruk: Sclérodermie avec hémiatrophie de la face, Rev. neurol. **25**:71 (Jan.-Feb.) 1918.

73. Levin, O. L.: Hemiatrophia Facialis, Arch. Dermat. & Syph. **1**:457 (April) 1920.

74. Osborne, E. D.: Morphea Associated with Hemiatrophy of the Face, Arch. Dermat. & Syph. **6**:27 (July) 1922.

75. Petrillo and Oreggia: Hemiatrophia facialis, Arch. latino-am. de pediat. **21**:696, 1927.

76. Wolff, H. G., and Ehrenclou, A. H.: Trophic Disorders of Central Origin: Report of a Case of Progressive Facial Hemiatrophy Associated with a Lipodystrophy and Other Metabolic Derangements, J. A. M. A. **88**:991 (March 26) 1927.

77. Wolff, H. G.: Progressive Facial Hemiatrophy: II. Report of a Case with Other Signs of Disease of the Central Nervous System, Arch. Otolaryng. **7**:580 (June) 1928.

ture bearing out this contention, and Marburg who did not share Cassirer's opinion expressly stated that as a rule the skin does not present a cicatricial or sclerodermal aspect, but, on the contrary, is perfectly smooth and freely movable. In the section on differential diagnosis, Marburg remarked that in scleroderma the lesions occur in different parts of the body, that the patches exhibit the three consecutive stages of edema, induration and atrophy, and that the occurrence, side by side, of recent and old plaques is a frequent observation. Without any desire to recapitulate the various clinical features of so well known a disease as scleroderma, we would add that this condition affects predominantly persons in the fourth and fifth decades of life, and its manifestations are usually symmetrical. Instances of strictly unilateral scleroderma are rare (cases of Afzelius, Pelizaeus, Steven, Knapp and others) and have already been mentioned under the caption of total hemiatrophy. It is to be pointed out, moreover, that in the majority of cases of total hemiatrophy associated with scleroderma, the sclerodermal lesions were confined either to the lower limb or to the trunk or to both, while the face itself, though markedly atrophied, did not exhibit truly sclerodermal characteristics (the cases of Knapp, Stief, Sádor and Tanka and Trepte, and L. Cerni's case 2). A careful perusal of some of these observations leaves one in doubt as to whether they were instances of scleroderma at all. There is no question that some cases of facial hemiatrophy described in the literature were actually of sclerodermal nature and fulfilled all the requirements of the most critical and skeptical observers. It is therefore evident that in certain instances the differentiation between the two may be absolutely impossible, but we do not think that, relatively common as it is, the association of scleroderma and facial hemiatrophy is adequate proof of their identity. There are other associations in the domain of neurology which have not given rise to such radical conclusions, and to mention only some of the more common we may cite the frequent association of migraine and epilepsy and of migraine and trigeminal neuralgia (noted in 20 per cent of Patrick's series of 200 cases). In the domain of more definitely organic neurology we would call attention to the not uncommon occurrence of exophthalmic goiter in tabes dorsalis, the association of Friedreich's disease and chronic degenerative (Huntington's) chorea.

Trigeminal Theory.—This theory received its strongest support from the histologic observations in the case of Mendel and that of Loebl and Wiesel, previously described in this paper. The so-called neuralgic pains, which are common enough, were said by Cassirer, Marburg and many others almost never to have the intensity of the pain occurring in typical trigeminal neuralgia, and in view of what recently has been learned about atypical neuralgia and the syndrome of vascular pain one

surely may doubt that all of such pains actually were of trigeminal origin. However, this cannot apply to cases presenting obvious clinical signs of lesions of the gasserian ganglion or of its peripheral divisions. Hyperesthesia, tender trigeminal points and pain on electrical stimulation of the nerves and muscles possess no significance whatever in favor of the trigeminal theory, and are fully explained by the loss of protective coverings resulting from the disappearance of the subcutaneous fat and connective tissue. In favor of the trigeminal theory are those cases more or less strictly confined to the area of distribution of one or more of the peripheral branches of the fifth nerve, such as those reported in the older literature by Denig, Estor, Kahler, Mauclaire and Strasburger (listed in Marburg's bibliography) and the more recently published cases of Wilfred Trotter,[41] G. Verrotti,[71] Weekers,[78] Boguslawski[18] H. G. Wolff,[77] van Bogaert and Helsmoortel,[12] Mezzatesta[79] and H. Lauber.[67] In some of these cases, moreover, there were additional features, such as recurrent herpes, recurrent iridocyclitis, neurokeratitis paralytica, marked atrophy of the cornea and conjunctiva, partial cataract and even optic atrophy of greater or less degree. Some, but surely not all, of these complications are imputable to involvement of the trigeminus alone.

Even more important are the cases presenting definite objective sensory losses in the integument innervated by the trigeminal nerve. Instances of this sort are far from common, but deserve adequate consideration. In the earlier editions of his textbook, Oppenheim mentioned 2 cases in which he found anesthesia, although it was not confined to the trigeminal distribution. Marburg said that in his case sensation was impaired in the domain of the mandibular division, and he further stated that diminution of tactile or pain perception was present in the cases of Mendel, Otto Kracht,[62] Heinemann, Donath and Jendrassik. The cases of B. Sachs,[60] Krueger[19] and Bönheim,[59] in all of which objective sensory losses were noted, have already been described. In the newer literature, the cases of Boguslawski,[18] van Bogaert and Helsmoortel[12] and Stiefler[17] deserve a brief description.

Boguslawski's patient, a man, aged 22, who had sustained a craniofacial traumatism in childhood, had suffered ever since with severe neuralgic pains in the distribution of the ophthalmic division of the right trigeminal nerve. In his twentieth year, a facial hemiatrophy developed in the corresponding region and involved the skin, the subcutaneous fat and the bony structure. The skin exhibited a somewhat cicatricial aspect, and the eyebrow was practically wanting. In addition to hyperalgesia there existed a paradoxical diminution of tactile and thermal sensibility.

78. Weekers: Hémiatrophie faciale et symptomes oculaires, Rev. neurol. **28**: 1154, 1921.

79. Mezzatesta, F.: Emiatrofia facciale e disturbi visivi, Riv. oto-neuro-oftal. **4**:315, 1927.

Van Bogaert and Helsmoortel's case was that of a man, aged 74, whose first symptoms consisted of crises of pain in the left frontotemporal region, extending occasionally to the side of the nose and the superior maxilla, accompanied by swelling of the eyelid and nasal hydrorrhea. Objectively, he presented an atrophy of the skin and subcutaneous tissue, most marked in the domain of the ophthalmic division of the fifth nerve, although encroaching somewhat on the area supplied by the maxillary division. The supra-orbital nerve was markedly sensitive to pressure. A complete Horner's syndrome existed on the affected side, and an anesthesia for tactile and thermal sense occupied the greater part of the distribution area of the ophthalmic division of the trigeminal. The lateral half of the cornea was hypesthetic. A hyperemia of the conjunctiva with decided lacrimation likewise was present. Following the injection of alcohol into the sphenopalatine ganglion there was a marked diminution of the algesic and secretory phenomena. The authors envisaged their case as a syndrome of the ophthalmic nerve and ocular sympathetic.

Stiefler's case was that of a man, aged 67, who twelve years before had sustained an injury to the right side of the forehead and temple and was unconscious for several hours, with bleeding from the right ear and vomiting. The patient had severe headache and vertigo for several days, and later complained of pains throughout the right side of the face accompanied by lacrimation on the same side which persisted for several weeks. After from six to eight weeks he noticed a depression under the right orbital margin which rapidly deepened and extended to the malar region, the side of the nose and the angle of the mouth and eventually reached the forehead. Objectively he presented an obliquely vertical groove on the cheek and forehead resembling the "coup de sabre" of French authors. The skin was almost as thin as paper and thrown into fine folds, and there was a marked disappearance of subcutaneous fat and connective tissue. The eyeball was deeply sunken and the palpebral fissure narrowed, but the right pupil was wider than the left. There was no involvement of the ear, tongue, palate or larynx, and no abnormal pigmentation. The hairs of the outer segment of the eyebrow and the beard on the affected side were much less abundant than on the left. Lacrimal secretion was equal on the two sides. There was slight impairment of tactile, pain and thermal sensibility in the distribution of the trigeminal nerve, more particularly in the domain of the first and second divisions. The skin of the face was drier on the right than on the left. Despite what is stated in the foregoing, the author stated that no sign of sympathetic disturbance existed clinically nor could any be demonstrated by the various pharmacologic tests. In summing up, Stiefler stressed the occurrence in his case of the prodromal period of genuine trigeminal neuralgia, the sensitive trigeminal points (supra-orbital and infra-orbital), the objective sensory deficits in all three branches of the trigeminal, and the limitation of the atrophic process to the area of distribution of this nerve.

Stiefler concluded that at the time of injury there occurred not only a cerebral concussion but a trauma of the base of the skull with involvement of the gasserian ganglion, as was indicated by the bleeding from the right ear (no mention was made of roentgen confirmation). The author doubted that the sympathetic system conveys trophic fibers, and it would have to be proved that the carotid plexus was injured simultaneously with the trigeminal. One could with equal right incriminate a lesion of the parasympathetic fibers, all the more so because it is known

that peripherally the latter fibers actually course in the trigeminal trunk and represent the "bulbar autonomic system." Furthermore, a lesion of the parasympathetic component would account for the trophic changes in the face more readily than involvement of the sympathetic division which follows the course of the peripheral vessels. The dilated pupil on the affected side is attributed to the fact that several years prior to the onset of the hemiatrophy the right eyeball was injured by a flying particle of iron or steel.

Although admitting that his case agrees with the trigeminal theory of Mendel, Loebl and Wiesel, Stiefler nevertheless maintained that the hemiatrophy results from involvement not of the trigeminal fibers but of the parasympathetic fibers which course with them.

Such are the circumstances that attended the birth of the parasympathetic theory of facial hemiatrophy. The interpretation of the observation contains so much that is contradictory and speculative that one could easily spare himself the task of making any comment. It is rather astonishing that a traumatic lesion of the gasserian ganglion should have given rise neither to herpes nor to keratitis and occasioned only a slight impairment of superficial sensation in the territory supplied by the trigeminal nerve. It likewise may be stated that, aside from a large part of the vasomotor fibers which do travel in the periarterial sheaths, the secretory, pilomotor and oculopupillary components of the cervical sympathetic, according to Langley and André-Thomas, after emerging from the superior cervical sympathetic ganglion pursue their course in the carotid plexus and join the trigeminal trunk at the gasserian ganglion, and remain inherent components of its three peripheral divisions. Finally, the negative results of the pharmacologic tests do not suffice to settle the issue. In summarizing the interesting case of Léri [11] it was pointed out that despite the presence of obvious sympathetic disturbances, the pharmacologic tests gave no information of value.

If we have related Stiefler's case so fully it was for the purpose of disposing, once and for all, of the so-called parasympathetic theory which to us appears totally untenable. While we do not question the accuracy of the foregoing observations or the claim that facial hemiatrophy does develop in connection with lesions of the trigeminal nerve, we would emphasize the fact that this occurs only when the lesion, whether central or peripheral, is so located as to involve the trigeminal and sympathetic systems at some point where both are in immediate juxtaposition. It was originally pointed out by Stier that operations on or removal of the gasserian ganglion never give rise to facial hemiatrophy, and this statement has been made by other writers (Wartenberg, Wolff and Ehrenclou, Paul Mauthey). Since the introduction of the newer method of retrogasserian section, total or subtotal, as practiced

first by Frazier and since then by many American surgeons, and despite statistics that in some quarters now mount into the hundreds, we do not recall any mention of facial hemiatrophy as a subsequent complication. Finally, it has been stated already that facial hemiatrophy not only extends beyond the confines of the trigeminal fields but that, not infrequently, it starts below the mandible in the cervical region. We need not draw from the literature to substantiate this fact, but simply recall that this was true in our cases 1 and 3.

Sympathetic Theory.—Originally proposed in 1875 by Seeligmüller, who incriminated more particularly a lesion of the cervical sympathetic, and followed by Jaquet, Bouveyron, Oppenheim and countless others, the sympathetic theory, which we regard as the only valid one, has the great advantage of being supported by the known facts of anatomy and pathology as well as of clinical observation. Marburg, who was skeptical because the sympathetic disturbances so frequently recorded indicate in some cases an irritative and in others a destructive process, nevertheless mentioned with admirable sincerity a very large number of observations definitely favorable to the cause of the cervical sympathetic. He referred to ten authors who observed mild exophthalmos and widening of the pupil, to six clinicians whose patients had a full-fledged Horner's oculopupillary syndrome and to seven others whose cases presented sensitive or swollen cervical sympathetic ganglia on the affected side. In the so-called symptomatic group, Marburg referred to Tournaire's [52] series of 5 cases of brachial plexus paralysis (Klumpke type) in which facial hemiatrophy and Horner's syndrome existed on the same side; to 7 cases of syringomyelia, in 3 of which (H. Schlesinger, Dejerine and Mirallié, Queyrat and Chrétien) Horner's syndrome was present in addition to facial hemiatrophy. He likewise recalled that in Jolly's case of multiple sclerosis with facial atrophy and in the cases of Mendel and of Loebl and Wiesel, already described in the present paper, advanced pulmonary tuberculosis was found at necropsy. Incidentally, he made capital of the fact that many cases of cervical sympathetic paralysis evolve without developing facial hemiatrophy, and particularly referred to a patient in whom Förster sectioned the fifth cervical to the first thoracic root (inclusive) and who at the end of a year exhibited no evidence whatever of hemiatrophy. Later, we shall endeavor to offer a plausible explanation for this apparent paradox.

Wartenberg has relatively little to say about the occurrence of cervical sympathetic disturbances in facial hemiatrophy and, like Marburg, thought that all cases presenting obvious signs of either trigeminal or sympathetic involvement are to be regarded as "symptomatic hemiatrophies" and should be separated entirely from the group of genuine "idiopathic hemiatrophies," although both authors admitted

that no essential difference exists between the two groups so far as the clinical physiognomy of the hemiatrophy itself is concerned. While it may be useful to conserve this classification on purely clinical grounds, the distinction should disappear entirely when it comes to a discussion of pathogenesis. In fact, there is perhaps no safer means of reaching a legitimate conclusion than by confronting so-called essential or idiopathic with symptomatic syndromes. The lessons already learned in connection with epilepsy, narcolepsy, progressive muscular atrophy, the parkinsonian syndrome and still other symptom complexes should suffice to convince one of the futility of clinging to the purely arbitrary classifications of earlier times, and it is rather astonishing that as late as 1925 Wartenberg should still hold fast to a crumbling pathogenic edifice. This is all the more true because a large number of cases of facial hemiatrophy on record strictly belong neither to the idiopathic nor to the symptomatic group, but supply the missing link demonstrating their common pathogenesis.

We are able to furnish the details of a considerable number of observations which serve to establish beyond a doubt that facial hemiatrophy frequently results from involvement of the cervical sympathetic alone, and likewise the records of several cases which, although instances of disease of the lower cervical roots, cervical cord or bulb, nevertheless demonstrate conclusively that this system is responsible for the trophic disturbance. Some of these observations apparently were overlooked even by Cassirer and Marburg; others have been published within the last few years. As most of them are extremely instructive, we believe that a brief description should be of interest. As examples of direct involvement of the cervical sympathetic chain, the following merit especial mention.

Heiligenthal[80] reported 2 cases in which facial hemiatrophy resulted from compression of the cervical sympathetic by a much enlarged thyroid gland. Similar cases have since then been observed repeatedly.

Ascher[8] reported a case due to compression by a cervical rib. His patient, aged 43, gave a history of a syphilitic infection twenty years before. Weakness of the little finger of the right hand appeared three years before he came under observation; this soon extended to the other fingers as well as to the muscles of the forearm and was accompanied by progressive wasting of the involved muscle groups. The man was compelled to give up his occupation as a shoemaker. Subsequently he developed motor weakness in the left arm having all the characteristic features of serratus magnus palsy. For several weeks he complained of pain in the neck and in the left arm and forearm. On examination there was marked atrophy of the thenar and hypothenar eminences and the interossei and forearm musculature on the right side, with the electrical reaction of degeneration. Objective sensory losses and circulatory disturbances were not observed in this

80. Heiligenthal: Beitrag zur Pathologie des Halssympathicus, Arch. f. Psychiat. **33**:77, 1900.

extremity. On the same side a facial hemiatrophy was present, and the palpebral fissure as well as the pupil were decidedly narrower than on the left side. Hyperemia and hyperhidrosis were not observed on either side of the face. On both sides a sensitive bony ridge, connected posteriorly with the seventh cervical vertebra and fusing anteriorly with the first rib, was easily palpable. The author concluded that there was a bilateral cervical rib with involvement of the cervical sympathetic on the right side only.

Kurt Mendel[9] presented at the Berliner Gesellschaft für Psychiatrie und Nervenkrankheiten on March 14, 1914, a woman, aged 53, who had noticed two years before a progressive wasting of the left side of the face. She complained of pain above the left eye, tinnitus and impaired hearing on the left. Under emotional circumstances or as the result of bodily exertion, flushing and sweating occurred only on the right side of the face. Whenever she had coryza, the left side of the nose ran more than the right. On examination it was found not only that coughing repeatedly on command and various tests requiring bodily exertion produced hyperemia and hyperhidrosis exclusively on the right side of the face but that the surface temperature was definitely higher on the right side. A classic Horner's syndrome was present on the left side. A decided enlargement of the thyroid, more marked on the left side, was noted, and roentgenograms revealed that the left half of the thyroid was occupied by a sausage-shaped bony structure that appeared as a deep-seated shadow in the proximity of the cervical spine. Mendel concluded that the cervical sympathetic was compressed between this ossified thyroid and the cervical vertebrae.

Oppenheim repeatedly referred to the case of Minor in which the extirpation of much enlarged cervical lymph glands was followed by facial hemiatrophy on the same side.

Claude and Cantraine[81] related the case of a man who, at the age of 12 years, had sustained extensive burns of the left arm and left side of the neck as the result of contact with electrical wires. The cicatrix on the neck was 6 cm. in width, was located 5 cm. below the inferior border of the mandible and extended from the midline in front to the anterior border of the trapezius muscle. There was complete facial hemiatrophy on the left side associated with a classic Horner's syndrome. The authors thought that there can be no question about the cervical sympathetic origin of certain facial hemiatrophies.

Cassirer,[82] the great advocate of an unlocalizable lesion of the vasomotor system, reported a typical instance of facial hemiatrophy which developed in connection with a malignant tumor (sarcoma) of the third to the fifth cervical vertebrae. The involvement of the cervical sympathetic cord surely cannot be denied in such a case.

Brüning and Stahl[83] quoted the case of a patient who had been injured in various parts of the body in the course of an affray and soon developed facial hemiatrophy. They subsequently had the opportunity of examining histologically the cervical sympathetic cords and found, on the affected side, a marked lympho-

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81. Claude, H., and Cantraine, E.: Hémiatrophie faciale par lésion du sympathique cervical et dilatation primitive de l'oesophage, Rev. neurol. **25**:187 (March-April) 1918.

82. Cassirer: Ueber Nachbarschafts und Fernsymptome bei Verletzung des Halswirbelsaüle und des Halsmarks, Deutsche Ztschr. f. Nervenh. **58**:52, 1918.

83. Brüning and Stahl: Die Chirurgie des vegetativen Nervensystems, Berlin, Julius Springer, 1924.

cytic infiltration of the sympathetic ganglia without appreciable degenerative changes in the ganglion cells.

L. Cerni's [58] case associated with extensive involvement of the cervical sympathetic cord already has been described in connection with the rôle played by pulmonary tuberculosis.

Trömmer's [65] case 2 concerns a girl 17 years of age, who underwent four operations for suppuration of the right middle ear. Following the last operation (radical mastoid) a facial palsy appeared which subsequently cleared up, while a facial hemiatrophy involving the skin, subcutaneous tissues and bone (confirmed by roentgenograms) gradually developed, as well as a lingual hemiatrophy. The right eyebrow was scantier than the left, and signs of sympathetic irritation were present on the right side (prominence of the eyeball and widening of the pupil). That the cervical sympathetic cord was injured in the course of the operation seems probable.

Paul Mathey [22] reported the case of a man, 26 years of age, who developed a right facial hemiatrophy six months after a thyroidectomy. All structures participated in the atrophy: skin, subcutaneous fat and connective tissue, facial and lingual musculature and bone. The hair, eyebrow and eyelashes turned gray and were less abundant than on the left side. A complete Horner's syndrome was present, the lacrimal secretion was less marked on the right side and the face on the same side was pallid and did not sweat either spontaneously or under artificial stimulation. No difference existed between the two sides as regards pigmentation and surface temperature. The right sternocleidomastoid muscle was atrophied, but exhibited normal electrical reactions, as did the atrophied facial and masticatory musculature. The right side of the neck exhibited the same color, secretory and other anomalies as the corresponding side of the face. It was postulated by the author that the cervical sympathetic nerve was injured in the course of the surgical intervention. Mauthey quoted Kaelin who, from a survey of the literature comprising 1,196 cases of thyroidectomy, found this nerve to have been injured in 12 cases, in none of which, however, did hemiatrophy develop. He likewise called attention to the fact that facial hemiatrophy has not been reported following complete section of the cervical sympathetic, but that injury to or compression of this structure apparently is the factor concerned in most cases thus far attributed to lesions of the cervical sympathetic. It should be added that Mauthey stated that his patient apparently had bilateral pulmonary tuberculosis, which naturally may have played a part in the genesis of the facial hemiatrophy.

In the group of facial hemiatrophies due to lesions of the roots of the brachial plexus or to intramedullary lesions of the cervical cord and bulb, we are able to add to the list of cases so conscientiously described in Marburg's monograph a few important observations that we have not found mentioned in the more recent publications

Ingelrans [84] related the case of a girl, aged 5 years, who presented a right brachial paralysis due to birth trauma. There was atrophy of the musculature and bony structures of the right arm and, in addition, a right facial hemiatrophy with flattening of the cheek and marked diminution in the size of the superior maxilla and mandible. No vasomotor or pigmentary anomalies were noted, but an incomplete Horner's syndrome was present.

84. Ingelrans: L'hémiatrophie faciale dans les paralysies radiculaires du plexus brachial, Écho méd. du nord **16**:609 (Dec.) 1912.

Dejerine and Krebs [63] described the case of a patient presenting a radicular brachial paralysis of the right arm dating back to an injury sustained during childhood, associated with a right facial hemiatrophy and Horner's syndrome as well as with objective sensory losses (hypesthesia for tactile, pain and thermal stimuli) in all three branches of the right trigeminal nerve. The authors attributed the facial hemiatrophy to a lesion of the central sympathetic tract within the cervical cord and the trigeminal hypesthesia to the concomitant involvement of the adjoining descending root of the fifth nerve which is known to course downward to the fourth cervical segment. A diagnosis of hematomyelia was made.

Trabaud [64] reported the interesting case of a soldier who was struck by a piece of shrapnel which penetrated into the right carotid region. Following its removal the next day, the patient experienced weakness in the left arm and leg and difficulty with micturition. On examination a month later, there was definite atrophy of the entire left side of the face without signs of facial palsy; the left eye was less prominent (enophthalmos) than the right, but the left pupil was much larger than its fellow. The left hand was hyperemic and warmer and moister than the right, and there was a slight diffuse atrophy of the left upper extremity, which likewise was the seat of an intention tremor. Fibrillations were noted in the musculature of the left shoulder. There was hypesthesia for pain and temperature in the greater part of the affected limb. In the left lower extremity the tendon reflexes were increased. The author concluded that there was an intramedullary lesion (hematomyelia) in the left side of the lower cervical cord involving the central sympathetic fibers as well as the ventral horn cell groups and the fibers for pain and temperature prior to their decussation.

Roger, Reboul-Lachaux and Montagnier [20] presented the case of a woman who exhibited atrophy of the small muscles of the left hand, dissociation of sensation (loss of pain and thermal sense) over the hand and anterior aspect of the left forearm, loss of tendon jerks in the left upper limb and increased tendon jerks in the left lower limb. In addition, the face on the same side presented sympathetic disturbances characterized by a facial hemiatrophy involving both the soft parts and the bony structures, loss of sweating and a dissociated Horner's syndrome (narrowing of the palpebral fissure, enophthalmos and dilatation of the pupil). Finally, there were a mild cervicothoracic scoliosis and a marked enlargement of the transverse process of the seventh cervical vertebra on the left side. The authors believed that they were dealing with an atypical or unilateral syringomyelia. This diagnosis surely is warranted by the observations.

Jelliffe and White [85] reproduced in their textbook a picture of Hammond's celebrated case in which facial hemiatrophy was the first manifestation and Morvan's syndrome the second episode in the eventual development of a classic picture of syringomyelia.

Hanse [13] (case 2) referred to a man, aged 51, giving a history of syphilitic infection, who presented a left facial hemiatrophy and in addition a pronounced atrophy of the interossei of the left hand. The Wassermann reaction of the blood was positive. The author attributed the clinical picture to a lesion of the ventral horn cells of the lower cervical cord (eighth cervical and first dorsal segments) encroaching on the lateral horn adjacent to the ciliospinal center.

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85. Jelliffe and White: Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1919, p. 328.

Other instances could be related, but it is believed that the foregoing suffice to establish that, in the realm of pathology, involvement of the central pathway of the cervical sympathetic is competent to condition the development of facial hemiatrophy and further to prove that the latter pathway courses in the immediate proximity of the pathway for superficial sensation.

Korn,[4] whose admirable thesis dates back to 1910, had correctly envisaged this problem when he upheld in brilliant fashion the cervical sympathetic origin of facial hemiatrophy. He maintained that the lesion could be localized according to the occurrence of oculopupillary signs on the one hand and trigeminal symptoms (pains, objective sensory losses, etc.) on the other, claiming that the two groups of symptoms practically never coexist (*this last statement suffers many exceptions*). He believed that the process might involve the sympathetic fibers peripherally in their course with the trigeminus, thus explaining the cases in which the hemiatrophy is confined to one or two divisions of this nerve trunk, or, more proximally (the cervical sympathetic cord and its ganglia), accounting for cases in which the facial hemiatrophy is more uniform or complete. Likewise the lesion could involve the central sympathetic fibers within either the cervical cord or the brain stem and thus explain the occurrence of the syndrome in connection with syringomyelia, syringobulbia, multiple sclerosis and other diseases similarly located. This hypothesis, fully mentioned by Cassirer in his monograph, is belittled if not ridiculed by him, but to our minds Korn's interpretation is the most logical thus far proposed, and our own conclusions are in large measure identical with his. Korn's own case is not devoid of interest; only the salient features need be mentioned.

A right facial hemiatrophy was accompanied by a typical Horner's syndrome and generalized pallor of the face on the affected side. The skin was cooler and drier than on the left side, did not flush on active exertion or exposure to heat nor did it exhibit appreciable sweating in contrast with the left. The eyebrow was much less developed than on the left side, and swollen and sensitive cervical glands were present on the right side.

From the anatomic standpoint, evidence is not wanting to support the contention that most cases of facial hemiatrophy are due to involvement of the cervical sympathetic. André-Thomas, an outstanding authority on the sympathetic nervous system, in his remarkable report at the International Neurological Reunion in Paris in 1926, after furnishing a loyal account of the anatomophysiologic and experimental studies of earlier investigators, reached a number of important conclusions which we consider it a duty to incorporate in this paper.

The sympathetic system presides over vasomotor, pilomotor and secretory functions. In its cervical division it not only regulates sudoral activity, but exerts some

influence on the lacrimal, meibomian and ceruminous glands and, in addition, conveys the oculopupillary contingent. The sympathetic, perhaps, is concerned also with pigmentation.

The superior cervical sympathetic ganglion receives preganglionic fibers from the first to the fourth (and occasionally from the fifth) thoracic spinal roots and innervates the head and neck. The inferior cervical ganglion receives preganglionic fibers from the fourth to the seventh thoracic spinal nerve roots and innervates the upper extremity.[86]

The vasoconstrictor fibers for the face and head do not have a uniform course and possibly the periarterial plexus is reenforced by fibers derived from the nerve trunks. It is through the cervical sympathetic cord that the pilomotor fibers for the face and head travel and not along the blood vessels, a fact already demonstrated by Langley. It now seems established that the secretory or sudoral fibers pursue the same course. From the superior cervical ganglion, fibers (postganglionic) emerge for the upper four cervical nerves and for the trigeminal trunk. The fibers destined for the latter, including the oculopupillary fibers, join the carotid plexus and the sympathicogasserian anastomotic loop and continue with the peripheral divisions of the trigeminus. The oculopupillary fibers course in the ophthalmic division of the fifth nerve, the nasal nerve and the long ciliary nerves. If the sympathetic cord is interrupted above the inferior and middle cervival ganglia, the sudoral and pilomotor areflexia occupies the whole domain of the superior cervical roots and of the trigeminal nerve. If it be involved above the superior cervical sympathetic ganglion, the sympathetic syndrome is confined to the trigeminal distribution (oculopupillary, vasomotor, pilomotor and sudoral syndrome of the trigeminal zone).[87]

In a few cases of a destructive lesion of the cervical sympathetic of congenital origin a craniofacial asymmetry, more or less pronounced, was noted. In young dogs, section of the cervical sympathetic stunted the development of the face, cranium and ocular globe on the corresponding side. In congenital lesions of the cervical sympathetic, heterochromia (loss or diminution of pigment) of the homolateral iris has repeatedly been observed.

In paralysis due to lesions of the plexus or nerve trunks an irritative sympathetic syndrome characterized by pilomotor hypertonia, hyperhidrosis, pains and spasm or contracture of striated muscles is commonly observed. The vasomotor reactions are variable; there may be either vasoconstriction or vasodilatation. Permanent vasodilatation and hyperthermia are more common in the irritative than in the paralytic syndromes due to peripheral nerve lesions.[88]

Facial hemiatrophy (cases of Chabanne, Schlesinger, Dejerine and Mirallié) has been attributed to a lesion of the sympathetic fibers originating in the ciliospinal center or of the descending bulbospinal sympathetic pathway. In the case of Dejerine and Mirallié (the patient whom André-Thomas personally examined) the existence of vasomotor disturbances was demonstrated by the greater intensity, on the affected side, of the hyperemia provoked by application of the galvanic electrode.[89]

From the foregoing deductions of André-Thomas, which surely withstand all adverse criticism, it at once becomes evident that the so-called

86. André-Thomas (footnote 46, p. 825).
87. André-Thomas (footnote 46, p. 838).
88. André-Thomas (footnote 46, p. 858).
89. André-Thomas (footnote 46, p. 892).

cervical sympathetic represents, in reality, fully one half of the sympathetic system and might well be designated as the craniofaciocervicothoracobrachial division of this system were the term more euphonic and less cumbersome. At any rate, these anatomic and clinical data enable us to explain the fact that facial hemiatrophy, which so commonly extends beyond the confines of the trigeminal distribution, invading the neck, mastoid region, upper part of the thorax and a more or less extensive segment of the upper extremity, still remains strictly within the territory innervated by the cervical sympathetic. At the same time sufficient evidence has been adduced both by the relation of the so-called symptomatic hemiatrophies and by the clinical deductions of André-Thomas to relieve the skepticism of Marburg based on the concomitance of contradictory sympathetic phenomena in cases of facial hemiatrophy.

How shall we explain the occurrence of complete unilateral atrophy or so-called total hemiatrophy? The answer has already been given by Brissaud [90] and his pupils Calmette and Pages,[91] but has never received serious consideration. This brings us to the theory known as the *cephalic trophoneurosis theory*. Brissaud, having in mind the total or crossed hemiatrophies observed by Henschen, Marie and Marinesco, Lunz, Raymond and Sicard and others, regarded facial hemiatrophy as only a partial or segmental type of his "trophonévrose centrale" and predicated a lesion of the periependymal gray matter of the sylvian aqueduct and oral portion of the fourth ventricle, being strengthened in this belief by the occasional occurrence of facial hemiatrophy in connection with syringomyelia. Not only is this conception perfectly logical, but a number of cases mentioned in the present paper apparently confirm Brissaud's interpretation. In fact, a large number of cases of facial hemiatrophy reported, especially in recent years, have been attributed, some of them without rhyme or reason, to lesions of the diencephalic floor, lateral wall of the third ventricle or periependymal gray matter of the sylvian aqueduct. In other words, Brissaud's hypothesis has found considerable favor, but it is believed that the pendulum now has swung too freely in the opposite direction and we think that Brissaud's theory applies essentially to cases of total hemiatrophy for which there surely exists no more plausible explanation. A case in point is that reported recently by Vivoldo,[92] an instance of total hemiatrophy which, inadvertently, we failed to mention when discussing this particular group.

A man, aged 28, presented a striking left facial hemiatrophy with plaques of canities. The left half of the thorax and the left extremities likewise exhibited

90. Brissaud: * Maladies nerveuses, Paris, Masson & Cie, 1899, vol. 2, p. 376.

91. Calmette and Pages: * Un cas d'hémiatrophie faciale progressive, Nouvelle iconog. de la Salpêtrière **16**:26, 1903.

92. Vivoldo, A.: Sobre un caso de hemiatrofia de origen simpatico, Rev. med. de Chile **54**:1066 (Nov.) 1928; abstr., Rev. neurol. **36**:868, 1929.

definite though less pronounced atrophy. Painful and spasmodic phenomena were present throughout the atrophied regions. A syphilitic etiology was evidently concerned.

Vivoldo's observation is strongly suggestive of a lesion of the right hypothalamus encroaching on the ventral nuclei of the thalamus and giving rise to so-called central pains. That the more common facial hemiatrophy likewise may depend on a lesion of the ependymal region of the mesencephalon or metencephalon seems certain in a few cases (the cases of Langelaan,[44] Kirschenberg,[54] Krueger [19] and Léri [11]), but such cases are exceptional and it is difficult to conceive that lesions at a higher level can give rise to facial hemiatrophy as Wartenberg and others have assumed. This naturally hinges on the ignorance concerning the level at which the cervical sympathetic fibers become detached from the contingent destined for the trunk and lower extremity. To affirm his position, Wartenberg has suggested the possibility that a somatotopic subdivision of the trophic centers in the diencephalon may exist and, in order to account for the fact that in hemiatrophies the face is involved with such predominant frequency, he has invoked the principle of phylogenesis and ontogenesis, calling attention to the relative inactivity of the craniofacial segment as compared with the trunk and extremities during the developmental period of life. The latter assumption is not easy to reconcile with the fact already emphasized that facial hemiatrophy, in a considerable number of cases, has developed in middle and even in late life.

The next factor that requires an explanation is whether one is warranted in assuming that trophic cell groups and fibers actually exist and, if so, that they belong to the sympathetic system. That nutrition and growth of the body tissues depend on both blood supply and neurogenic influences hardly needs mention. The trophic influence of the central nervous system has long been recognized. The trophic control of the somatic musculature by the ganglion cell complexes giving origin to the cranial and spinal nerves is today universally admitted and well illustrated by acute anterior poliomyelitis, amyotrophic lateral sclerosis and other diseases. In acute anterior poliomyelitis there is a diffusely infiltrating inflammatory process involving not only the anterior horns but the lateral and posterior horns and even the white columns, and clinically there is more than muscular atrophy, namely, atrophy of the bones and vasculature, anomalies of the subcutaneous tissue (adiposity, trophedema), vasomotor and secretory disturbances, visceral ptosis, etc. While we are well aware that changes in the bones in part may be explained by functional inactivity (hysterical paralysis, surgical immobilization), as was amply demonstrated during the recent war, we do not believe that this factor alone suffices and we have seen cases of

poliomyelitis progressing to substantial recovery within a few weeks or months in which roentgenograms revealed definite skeletal changes in the affected limb. We likewise have seen 2 cases of hysterical paralysis of several years' duration presenting definite asymmetry of vasomotor and secretory function but in which careful measurements did not reveal material differences between the two sides as regards either the length or the circumference of the affected limb or limbs.

One of these cases was that of a woman, aged 23, who had been permitted to display a classic left hysterical hemiplegia since the age of 12.

The other case was that of a girl, aged 16, examined at a local hospital, who exhibited a complete spastic monoplegia of the right lower extremity which developed at the age of 8 years within a few days after a railway collision in which an older sister was killed.

The hemiatrophy occurring in connection with infantile hemiplegias already has been mentioned, and it is interesting to note that, in the large and heterogeneous group formerly designated as the "cerebral palsies of childhood," there are many instances of hemiathetosis in which the same stunting of growth of the affected extremities is observed as in frankly paralytic cases. We have the records of 3 cases of this kind exhibiting decided shortening and circumferential reduction despite the almost incessant overactivity of the corresponding musculature. It is well known that actual hypertrophy of the muscles is not rare in athetosis. Such observations clearly establish that some other factor, in addition to functional inactivity, is responsible for the atrophies encountered both in spinal and in cerebral lesions.

Returning to the trophic disturbances occurring in acute poliomyelitis, it should appear entirely reasonable to maintain that the various atrophies, other than the muscular, depend on involvement not of the motor ganglion cells but of entirely separate cell groups or fiber pathways, and one must instinctively think of the lateral horn and the tractus intermediolateralis. In certain diseases, likewise affecting the ventral horn cells but of purely degenerative nature, such as amyotrophic lateral sclerosis and so-called subacute or chronic poliomyelitis (for which term we would like to substitute that of progressive degenerative poliomyelopathy), we observe a strictly elective and progressive wasting of one muscle group after another. The occurrence of pains of causalgic type and vasomotor crises either resembling Raynaud's syndrome or assuming a reversed physiognomy has been described very well by van Bogaert,[93] but to the best of our knowledge no one has yet recorded atrophy of the skin, subcutaneous fat or bony structures in connection with amyotrophic lateral sclerosis or chronic poliomyelitis.

93. van Bogaert: Sclérose latérale amyotrophique avec troubles vasomoteurs et syndrome douloureux paroxystique, Rev. neurol. **31**:519 (Nov.) 1924.

It might be objected that these diseases appear much later in life than either acute poliomyelitis or facial hemiatrophy, but it is now well known that acute poliomyelitis no longer is an exclusively "infantile paralysis" and it has been reiterated here that facial hemiatrophy may develop at any age.

In a series of brilliant publications, L. R. Müller,[94] and his pupils, Goering [95] and Böwing,[96] assembled an imposing array of documents and discussed in minute detail this whole problem of trophism in an attempt to reach a truly scientific conclusion regarding the rôle played by the vegetative system and more particularly by its sympathetic division. Müller concluded that it is the sympathetic that is concerned with this function and that the trophic fibers course in part with the peripheral sensory nerve fibers and in part with the fibers accompanying the vascular apparatus. Goering, after referring to the view held by many authors that the trophic influences of the sympathetic system exert themselves through the medium of the vasomotor fibers, shrewdly remarked that the occurrence of facial hemiatrophy without vasomotor disturbances and, conversely, the occurrence of sympathetic disturbances including vasomotor symptoms without facial hemiatrophy show that the sympathetic, of necessity, must carry separate trophic fiber strands for the passive tissues of the face. Therefore the absence of all other sympathetic disturbances in some cases of facial hemiatrophy is no argument against the sympathetic origin of the syndrome. Moreover, the fact that in many cases of facial hemiatrophy, definite signs are present which indicate a lesion or injury of the cervical sympathetic affords the best evidence that special trophic vegetative nerve fibers exist.[97]

The intimate mechanism presiding over the development of facial hemiatrophy is not easy to establish. Many authors who hold the vegetative system and particularly its sympathetic division, whether in its peripheral or its central course, responsible for the syndrome assume a state of more or less permanent irritability of the sympathetic. Wartenberg even went so far as to say that in facial hemiatrophy one

94. Müller, L. R.: Vegetatives Nervensystem, Berlin, Julius Springer, 1920; Ueber den Einfluss des Nervensystems auf das Fettgewebe, Zentralbl. f. d. ges. Neurol. u. Psychiat. **25**:490, 1921.

95. Goering, D.: Ueber den Einfluss des Nervensystem auf das Fettgewebe, Ztschr. f. Konstitutionslehre **8**:313, 1922.

96. Böwing, H.: Zur Pathologie der vegetativen Funktionen der Haut, Deutsche Ztschr. f. Nervenh. **76**:71 and 307, 1923.

97. Goering's article contains pictures of the patients in two cases of facial hemiatrophy observed at the Medical Polyclinic in Würzburg, which have not been included in our count of reported cases because detailed clinical histories were not given.

may speak of "eine spastische Lähmung der niederen trophischen Zentren mit gesteigerter reflektorischer Erregbarkeit" (a spastic paralysis of the lower trophic centers with increased reflex excitability). This view is based largely on the fact that until recently the trophic fibers were considered either identical with the vasomotor fibers or else as coursing exclusively with them in the periadventitial sheaths of the peripheral blood vessels, and the occasional narrowing of the carotid and temporal arteries on the affected side in the cases of Bouveyron, Bergsohn and H. Wolff (mentioned in Marburg's monograph) undoubtedly had a share in promoting this interpretation. In the various observations briefly described in this paper both irritative and paralytic types of sympathetic disturbance have been mentioned, but the paralytic predominate by far, and, what is most important of all, practically in no case of facial hemiatrophy having sympathetic concomitants have the latter been exclusively of irritative or of paralytic type. Almost invariably the syndrome has shown some paradoxical feature, even to the dissociation of Horner's complex (mydriasis instead of myosis). This is the best proof that a completely destructive lesion of the sympathetic is not responsible for the occurrence of facial hemiatrophy and this is well borne out by the fact that in recent years, despite the wholesale extirpation of the lower cervical ganglion, section of the sympathetic cord and ramisection, facial hemiatrophy does not appear to have been observed in the subsequent histories. If progressive facial hemiatrophy is due to an irritative and not to a destructive type of lesion, it occupies a unique position and offers a strange contrast to the various syndromes resulting from lesions of the endocrine glands, structures intimately connected with the vegetative nervous system. Acromegaly, presumably due to hyperfunction of the hypophysis, is characterized by hypertrophic manifestations, while Simmonds' disease (hypophyseal cachexia) is associated with destructive or degenerative lesions of the hypophysis. Toxic hyperthyroidism, although giving rise to emaciation as the result of the much increased metabolic rate, is associated with signs of sympathetic irritation, while the converse syndrome, myxedema, presents striking signs of sympathetic depression (anhidrosis, hypothermia, dulling of emotional reaction, loss of hair, etc.). In facial hemiatrophy, while vasomotor secretory and oculopupillary signs may indicate either hypofunction or hyperfunction, the facial atrophy bears the stamp of a premature decay of the affected side. For these various reasons, we believe that the condition is due to a lesion of mixed type, partly destructive and partly irritative (the equivalent of the newer "release phenomenon"), in which destructive component probably predominates.

Endocrine Theory.—Rothmann was the first to express the opinion that facial hemiatrophy might result from disease of the ductless glands,

this view being based on the occasional occurrence of the syndrome in patients presenting obvious signs of lesions of the hypophysis, thyroid gland or ovary. The association of facial hemiatrophy and acromegaly has been observed by Harbitz [98] and G. Bassi (mentioned by Marburg), and very suggestive signs are described in H. G. Wolff's third case.[23] The combination of facial hemiatrophy and exophthalmic goiter or other lesions of the thyroid already has been mentioned in connection with a series of cases illustrating direct involvement of the cervical sympathetic cord. In a publication on lipodystrophies, the first case described by Ziegler [14] is an instance of facial hemiatrophy developing in the course of repeated attacks of exophthalmic goiter. Some enlargement of the thyroid gland without definite signs of hyperthyroidism was mentioned in a number observations and was present in our case 2. Since anatomists describe separate filaments derived from the cervical sympathetic cord and winding around the thyroid arteries, and since Greving demonstrated the existence of a fiber bundle running from the nuclei of the tuber cinereum to the infundibulum and the posterior lobe of the hypophysis, it has become increasingly difficult correctly to appraise the respective rôles of the vegetative nervous system and the endocrine glands in the genesis of many of the so-called endocrine syndromes. That practically all the latter exhibit a prominent neurologic component is, of course, a clinical fact recognized from the first. However, it is believed that the association of endocrine disturbances with facial hemiatrophy has been altogether too rare to receive serious consideration.

Closely allied to the foregoing theory is the relationship of facial hemiatrophy to lipodystrophy. This point has been developed particularly by Wartenberg, who believed that a close link exists between the two. Calling attention to the fact that in many cases the skin is not involved and that it is chiefly the subcutaneous fat that disappears, that facial atrophy is bilateral in a fair number of cases and furthermore that the dystrophy in some cases extends to the neck, the upper part of the chest and even to the proximal segment of the arm, Wartenberg saw a gradual transition from facial hemiatrophy to Simons' progressive lipodystrophy. He further stressed the point that in the latter disease the skin and hair often show the same changes as in hemiatrophy. He finally referred to the interesting case reported by von Sarbo, in which the patient developed the syndrome of progressive lipodystrophy with typical striatal manifestations in the wake of epidemic encephalitis. That these analogies are interesting and sug-

98. Harbitz, F.: Akromegalie und Hemiatrophia facialis progressiva: Gleichzeitige Missbildungen mehrere Organe mit innerer Sekretion, Centralbl. f. allg. Path. u. path. Anat. **22**:801, 1911.

gestive is readily admitted, but we need only to point out that if facial hemiatrophy is sometimes bilateral, lipodystrophy, like the endocrine syndromes, is characterized by its bilaterality and symmetry and that to the best of our knowledge involvement of the bony structures does not occur. Wartenberg's views based primarily on his belief that facial hemiatrophy is due to a lesion of the diencephalic floor have made a decided impression, particularly in our own country, and are probably responsible for the rather astonishing theory recently advanced by H. G. Wolff [99] and Wolff and Ehrenclou [76] who had the good fortune to observe 3 cases of facial hemiatrophy, 2 of which are of exceptional interest.

After recalling the fact that facial hemiatrophy may be associated with scleroderma, alopecia, cerebral degeneration, convulsions, vasomotor dysfunction and many signs of autonomic imbalance, such as anisocoria, disorders of skeletal growth and fat metabolism, abnormal visceral sensations, emotional instability, etc., these authors reach the conclusion that facial hemiatrophy is not an entity but simply part of a syndrome of general autonomic imbalance resulting from disturbance of the vegetative apparatus located in the diencephalon or brain stem. In all 3 of their cases the patients complained of pains and aches in various parts of the body; the soft parts of the extremities were exceptionally sensitive to even slight pressure, and the skin itself presented definite or strongly suggestive evidence of scleroderma. Their first case is particularly interesting by reason of an associated progressive lipodystrophy, the only case recorded thus far in the literature, and it seems not unlikely that, inspired by the remarkable case of von Sarbo, this case dictated the terms of their conception of facial hemiatrophy and its pathogenesis. Wolff's third case is important from a triple point of view. The facial hemiatrophy was preceded by an infectious episode, which may have been epidemic encephalitis, and was followed some years later by the occurrence of both "grand mal" and "petit mal" attacks as well as by an enlargement of the hands and feet suggestive of acromegaly.

Interesting and instructive as are their cases, we do not believe that Wolff and Ehrenclou are justified in dumping over an already overcrowded diencephalic floor the many subjective discomforts complained of and the heterogeneous group of clinical disturbances mentioned by them, even though a few of these are known to have acquired legitimate residence in that particular region of the neuraxis. Such generalizations are hazardous and instead of clarifying the issue serve merely to befog one of the most elusive pathogenic problems in the realm of neurology.

99. Wolff (footnotes 23 and 77).

Although the larger publications on facial hemiatrophy usually include a brief reference to the opposite syndrome, facial hemihypertrophy, we have not seen fit to discuss this equally interesting though infinitely rarer type of dystrophy. The same applies to the occasional occurrence of facial hemiatrophy on one side and facial hemihypertrophy on the other. A case of this peculiar association recently has been reported by Sterling.[100]

TREATMENT

There is little to say under the heading of treatment which has not already been thoroughly covered. Gersuny's method of subcutaneous injection of melted paraffin as a prosthetic procedure is well described in Marburg's monograph as well as in some textbooks of surgery. The method is not free from danger, but has given excellent cosmetic results in a number of cases. Marburg stated that in one case the improvement in the patient's appearance was still definite after the lapse of eight years. We are much more interested in the effect that might be obtained by periarterial sympathectomy, already advocated by Cassirer. Wartenberg mentioned the fact that this operation has given encouraging results in some cases of scleroderma reported by Leriche, Förster, Brüning and others. Necessarily, periarterial sympathectomy should be resorted to in the earliest stage of facial hemiatrophy, which would imply its recognition from the start, and it is well known that in facial hemiatrophy the patient comes into competent hands only when the process already has reached a relatively advanced stage. Nevertheless, this operation surely is worthy of trial and incidentally might serve to throw considerable light on the problem pertaining to the almost generally assumed identity of the vasomotor and trophic nerve fibers. It would thus serve both a therapeutic and a pathogenic purpose.

SUMMARY

A diligent survey of the literature reveals that at least 400 cases of progressive facial hemiatrophy thus far have been reported. Among these, approximately 24 were instances of total hemiatrophy and 27 were cases of double facial hemiatrophy. That statistics are by no means an accurate index of the actual frequency of a given disease or syndrome is well known. An endeavor has been made to present a general description of facial hemiatrophy, and a number of features emphasized by earlier authors have been either confirmed or revised. The much greater incidence among females and the predominant involvement of the left side of the face have not been substantiated. Although appearing with especial frequency during the first two decades

100. Sterling: Hémihypertrophie et hémiatrophie faciale, Rev. neurol. **35**:296 (Feb.) 1928.

of life, the condition may develop at any age, even in advanced life. As a rule, facial hemiatrophy involves all the tissues (this is true in the 3 cases reported in this paper), but may spare the skin, much more rarely the bony structures; it perhaps affects most severely the subcutaneous fat and connective tissue. The atrophy of the musculature is entirely a matter of bulk reduction as shown by the retention of function and normal electrical responses. The wasting of the bony elements, while unquestionably more common in cases developing in early life, may assume equally pronounced proportions in older subjects. Although known as facial hemiatrophy, this peculiar dystrophy has in many cases extended to the neck, the upper part of the thorax and arm or even to the entire half of the body. Cases 1 and 3 are notable for the fact that the process initially developed in the domain of the second and third cervical roots. Alopecia, regarded by Oppenheim, Curschmann and other early writers as almost invariably absent, antedated all other manifestations by months or years in Wartenberg's case as well as in our case 3. The occurrence of pigmentary anomalies is not uncommon, while herpes, nevi and telangiectasis are rare. As regards vasomotor and secretory disturbances, it may be said that while they are common enough, they do not exhibit a uniform type, both deficient and exaggerated function having been observed in a large number of instances. The presence of trigeminal symptoms on the one hand and of oculopupillary signs on the other has been discussed fully under the heading of pathogenesis.

As regards etiologic factors, despite the strong plea entered by Wartenberg, we agree with Marburg that heredity and familial incidence are of such rare occurrence that they possess little significance. Admittedly difficult to evaluate correctly is the rôle played by infectious diseases, although in many instances the rapid development of facial hemiatrophy following immediately in the wake of a severe systemic infection cannot be ignored. Sterling's series of 4 cases has been described as an example taken from the recent literature. More important of all, however, is the presence of pulmonary tuberculosis in a strikingly large percentage of cases. The development of facial hemiatrophy in connection with a circumscribed infectious focus (angina, peritonsillar abscess, periostitis, etc.), while not common and altogether overemphasized by the earlier writers and more especially by Möbius, likewise deserves adequate consideration as such factors represent, in a certain measure, a spontaneously occurring trauma exerting perhaps much the same influence as external violence with the additional possibility of ascending perineural infection. While applicable only to a small proportion of cases, Möbius' hypothesis does not appear to us as ridiculous as others have attempted to represent it. A history of antedating traumatism is given in from 25 to 35 per cent of cases, and

unlike many authors we believe that it constitutes more than a localizing or concurrent factor and may be actually the sole etiologic factor, at least in those cases in which, as illustrated by case 1, the hemiatrophy begins to appear within a period of a few weeks or less.

When it comes to a proper evaluation of the various theories elaborated in order to provide a plausible pathogenesis for facial hemiatrophy, one enters a field beset with contradictions and almost invincible difficulties. Unquestionably the least easily disposed of is the sclerodermal theory which has gained such a firm footing. While we willingly admit that in many cases a distinction between the two diseases may be impossible and that scleroderma can reproduce in the faciocervical region a perfect image of facial hemiatrophy, we cannot agree with Cassirer and his numerous followers who proclaim the identity of the two diseases, and we already have given in detail our reasons for rejecting this theory. Regarding the trigeminal, the parasympathetic and the endocrine theories we believe that sufficient evidence has been furnished to prove conclusively that all three are totally untenable. The view of Wartenberg, who regarded an encephalitis of the diencephalic floor as the primary lesions responsible in his case and assumed that lesions of other or similar character in the same location would account for the cases of others, while admirably presented, has too little substantiation to be taken seriously. One forgets too readily that a disease like encephalitis, whether of epidemic or other type, is a diffuse process spreading its ravages in many other regions besides the mesencephalon, diencephalon and basal ganglia. Wolff and Ehrenclou's conception of facial hemiatrophy as simply one component of general autonomic imbalance, ingenious as it is, we regard as hazardous and likely to befog instead of simplify the problem. Before the views of Wartenberg and those whom he apparently has inveigled can gain real favor, we shall need a large number of necropsies followed by reliable topographic histologic studies. Brissaud's view of a cephalic trophoneurosis we believe to be entirely acceptable in so far as it applies to total and crossed hemiatrophies.

It is our conviction that the sympathetic theory alone affords a satisfactory explanation of the great majority if not the totality of cases of facial hemiatrophy thus far recorded. This opinion is based on the following facts, all of which are well established on either clinical, pathologic or anatomic grounds.

1. Lesions compressing or otherwise injurying the cervical sympathetic cord repeatedly have determined progressive facial hemiatrophy on the corresponding side. A number of examples purposely have been described in this paper, and it would have been easy to duplicate that number.

2. In the group of so-called symptomatic hemiatrophies (syringomyelia, hematomyelia, brachial plexus injuries, bulbopontile foci of encephalitis, etc.) a concomitant Horner's syndrome was present in the majority of cases, and not infrequently there were vasomotor and secretory disturbances as well.

3. Pulmonary tuberculosis is mentioned in a very large number of observations and was found in the 3 cases of so-called idiopathic facial hemiatrophy that thus far have come to necropsy.

4. The distribution of the postganglionic fibers of the cervical sympathetic ganglia is so extensive as to embrace the territory affected not only in the usual type of facial hemiatrophy but likewise in those cases in which the process extends to the base of the neck, the upper part of the thorax and the upper extremity. This anatomic detail is confirmed by the work of earlier anatomophysiologists and the recent researches of André-Thomas.

5. The extensive investigations of L. R. Müller and his pupils, Goering and Böwing, on the origin and distribution of the trophic fibers for the various peripheral tissues fully substantiate the claims of those who uphold the sympathetic theory.

6. In the 3 cases reported in the present article, facial hemiatrophy was accompanied by unequivocal signs of disturbed sympathetic innervation on the corresponding side.

7. While the preceding paragraphs apply to the cervical sympathetic alone, the total hemiatrophies are to be explained by the perfectly logical hypothesis of Brissaud and his pupils who incriminated a lesion of the fiber pathways coursing in the periependymal zone of the fourth ventricle and sylvian aqueduct, presumably fiber tracts located in the proximity of the motor nuclei of the cranial nerves (such as the "fasciculus longitudinalis dorsalis of Schütz"), the mesencephalic root of the trigeminal, the area adjoining the descending spinal root of the same nerve and the fasciculus solitarius.

It will be well in the future not to rely exclusively on the results of pharmacologic tests, which so frequently are misleading, in order to assert or deny the presence of sympathetic disturbances in cases of facial hemiatrophy, and to avail ourselves of the simple and invaluable clinical methods of exploration devised by André-Thomas. We have not the temerity to believe that we have succeeded any more than our predecessors in solving the puzzle of facial hemiatrophy, and we expect that flaws in our interpretation probably will be unearthed by subsequent writers. Our main purpose was to define as clearly as possible the unquestionably predominant rôle of the sympathetic system in the genesis of this most interesting dystrophy. We do not regard the condition as an entity in the sense that its clinical features are immutable

and its anatomopathologic substratum exhibits an unvarying character and location. Nevertheless it cannot be denied that the clinical physiognomy of facial hemiatrophy is relatively so uniform that it is recognizable at a glance, and while it may be conditioned by the most diverse lesions, the widely varying localization of such lesions is no argument against regarding it as a close approach to an entity for the excellent reason that the course of the sympathetic fiber system with its intercalated cell complexes (central and peripheral divisions) is an exceptionally long and intricate one. It is preferable to designate facial hemiatrophy as a well defined syndrome comparable in a large measure to a number of well recognized syndromes, e. g., the parkinsonian syndrome and the syndrome of pseudobulbar paralysis.

CONCLUSIONS

Progressive facial hemiatrophy is a well defined syndrome having distinctive clinical features, resulting from widely varying types of lesions which apparently involve in selective fashion the sympathetic division of the vegetative nervous system at some point in either its central or its peripheral course.

The condition is much more common than was formerly believed, may develop at any period of life and exhibits no material predilection for the female sex or for the left side as was maintained by classic authors.

The actual etiology of facial hemiatrophy still remains largely speculative, but it is believed that in many cases immediately antecedent infections and faciocervical traumas play an actual causative rôle.

Aside from its undeniably close relationship to scleroderma, which itself may be responsible for some cases, the various theories advanced to provide a logical pathogenesis, with the exception of the sympathetic theory, are believed to be totally untenable.

Three cases of typical facial hemiatrophy are presented in detail and all 3 exhibited unescapable evidence of disturbances in the domain of the cervical sympathetic system.

ABSTRACT OF DISCUSSION

Dr. Foster Kennedy, New York: In support of the idea of Dr. Archambault and Dr. Fromm, I wish to report a case that I saw in France, in which the situation was this: A gunner's left arm was severely wrenched by hanging on to a runaway horse. I saw the patient four weeks later. He suffered great pain in his left arm and particularly in his left hand. His condition was thought to be neuritic. On roentgen examination he was found to have a double cervical rib and a characteristic cervical rib syndrome in the left hand. There also developed Horner's syndrome on the left side and a well marked hemiatrophy of the left side of the face. I had no doubt at the time that he had compression of the left plexus and of the left cervical sympathetic by the cervical rib. Such a case supports Dr. Archambault's contention regarding the morbid pathology of this disease.

TRANSECTION OF THE SPINAL CORD IN THE NEW-BORN

A CASE WITH AUTOPSY AND COMPARISON WITH A NORMAL CORD AT THE SAME AGE *

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Reflex activities dependent on segments of the spinal cord below a transection have long been known and discussed in the physiologic laboratory, but recognition of similar phenomena in human beings was largely the result of the careful observations by Head and Riddoch [1] of a group of wounded men. These authors showed that if a sufficiently large segment of human spinal cord is isolated by a sharp transverse lesion it may, after a period of so-called spinal shock, become the seat of extensive reflex activity. Severe infection in the body, especially of the bladder or in bed sores, appeared to prevent or diminish such reflex activity. The reflexes were characterized by their tendency to spread over many segments of the cord, producing reactions in skeletal muscles, sweat glands and hollow viscera, such as the bladder and rectum. In all instances of transection proved to be anatomically complete, the movements produced in the skeletal muscles were limited to flexion of the lower extremities and trunk, whereas in the presence of an incomplete lesion of the cord it was often possible to elicit extensor responses. In the latter condition, the "mass reflexes" were less spreading, and in no instance did the reflex extend to cause voiding of urine.

Prior to the observations of Head and Riddoch,[1] a certain amount of reflex activity had been noted below spinal transections and commented on, especially by Walshe,[2] who thoroughly appreciated its significance. He did not have an opportunity to study the reflexes in their fullest development because the poor physical condition of most of his patients tended toward the early onset of "isolation dystrophy."

Injury to the spinal cord during birth has been thoroughly discussed by Crothers [3] and Crothers and Putnam [4] during the past decade. In their various articles are described several instances of spinal tran-

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* Read at the Fifty-Seventh Annual Meeting of the American Neurological Association, Boston, May 27, 1931.

1. Head, H., and Riddoch, G.: Brain **11**:188, 1917. Riddoch, G.: ibid. **11**: 264, 1917.

2. Walshe, F. M. R.: Brain **37**:269, 1914.

3. Crothers, B.: Am. J. M. Sc. **165**:94, 1923.

4. Crothers, B., and Putnam, M.: Medicine **6**:41, 1927.

section with reflex activity below the lesion. They also discussed the means by which injury to the spinal cord may take place during birth, and reviewed the literature on obstetric trauma to the spinal cord. They pointed out that, as early as 1870, a case of obstetric injury to the spinal cord with autopsy was described fully by Parrot,[5] who noted the presence of a flexion mass reflex on the third day of life. In 1925, Ford[6] reviewed the recent literature and published a description of six cases, one with a report of autopsy and a photograph of the spinal cord, and several in which there were elaborate reflex phenomena.

The present case was briefly reported a year ago,[7] but without the pathologic evidence that has since come to hand. A short summary of the clinical history, previously reported in full, follows.

REPORT OF CASE

History.—C. A., a white girl, born on Dec. 29, 1929, was admitted to the Infants' Hospital on April 15, 1930, because of weakness, fever and convulsions. Delivery, as described by the attending physician, was difficult and involved the conversion of a left shoulder anterior presentation into a breech presentation by manipulation. Just before delivery of the head, a prolapsed and nonpulsating cord was noted, and a rapid but easy extraction was performed under nitrous oxide and oxygen anesthesia. Respirations were established with difficulty, and it was noted at once that the baby was very weak. Respiration was always weak, as was the baby's cry. The legs never moved spontaneously, but "jerked up" if stimulated in any way. When this activity first appeared is unknown. At the age of 2 months, an infection developed, with a high temperature, for which no cause was found until two weeks later, when bilateral otitis media appeared. At about this time it was first noted that the right arm tended to assume a characteristic position. On two occasions, when about 3½ months of age, the baby had, in association with a high temperature, convulsive attacks limited to the face, neck, arms and diaphragm.

Physical Examination.—Save for intermittent mild cyanosis of the mucous membranes, examination gave negative results, except with respect to the nervous system. The palpebral fissure on the right was definitely narrower than that on the left. With this exception, no abnormalities were found in the head, neck or left arm.

The right arm was held abducted at approximately a right angle from the side, externally rotated at the shoulder and half flexed at the elbow, with the forearm in nearly complete supination, the wrist extended and the fingers flexed at the proximal row of interphalangeal joints over the loosely adducted and flexed thumb. There was marked atrophy of the small muscles of the hand.

There was no evidence of any activity of the intercostal muscles, respiration being entirely diaphragmatic and the thoracic cage partially collapsing with each inspiratory effort.

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5. Parrot, J.: Union méd. du Canada **11**:137, 1870.

6. Ford, F. R.: Breech Delivery in its Possible Relations to Injury of the Spinal Cord, Arch. Neurol. & Psychiat. **14**:742 (Dec.) 1925.

7. Byers, R. K.: New England J. Med. **203**:507, 1930.

The abdomen was soft and bulging, and the tone of the muscles was poor. No abdominal reflex was obtained above the umbilicus, but a sharp stimulus applied below this level caused a sudden weak contraction of the lower abdominal muscles.

The knee jerks and ankle jerks were easily obtained, were hyperactive and tended to be clonic. Ankle clonus and Babinski's sign were readily obtained on both sides. Sudden stimulation by pinching, pricking or stroking either sole produced sudden flexion of the leg, the knee being drawn up onto the body, which was occasionally accompanied by flexion of the opposite leg. Rarely, these stimuli caused abduction of the leg and thigh at the hip. Similar weaker reflexes could be

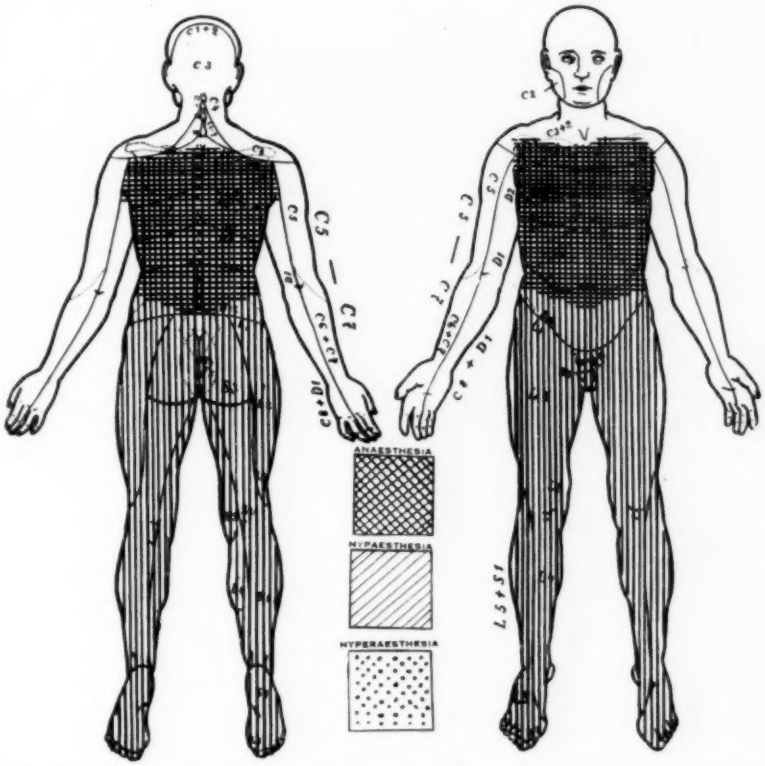

Fig. 1.—Diagram of the sensory changes. The small squares indicate areas of anesthesia; the vertical lines, areas of anesthesia plus reflex activity, and the white portions, normal areas.

obtained by noxious stimuli over the lower legs and thighs, though the farther from the sole the stimulus was applied, the more definitely noxious it needed to be to produce any response. Gentle pressure applied to the ball of the foot, especially if exerted so as to extend the toes, brought about a general rigidity of the leg, so that the hip and knee were extended and the ankle was slightly plantar flexed. This could be demonstrated equally on either side.

No voluntary movements of the right hand, trunk or legs were noted at any time.

Sensory examination was attempted only by pin prick. Over the head, neck, arms and upper borders of the shoulder girdle, down to the level of the clavicles in front

and to the upper borders of the scapulae behind, there was prompt appreciation of pain. Below this level there was no evidence of any conscious appreciation of the stimuli. Over a wide zone, extending from the clavicles to the umbilicus, pin pricks produced no response whatever, but below this level reflex activity as described resulted.

Urine could not be squeezed from the bladder by suprapubic pressure; the anal sphincter had good tone, and an active anal reflex resulted when an attempt was made to insert a finger into the rectum. On one occasion, in connection with the mass reflexes resulting from stimulation of a sole, urine was discharged from the bladder in a strong stream.

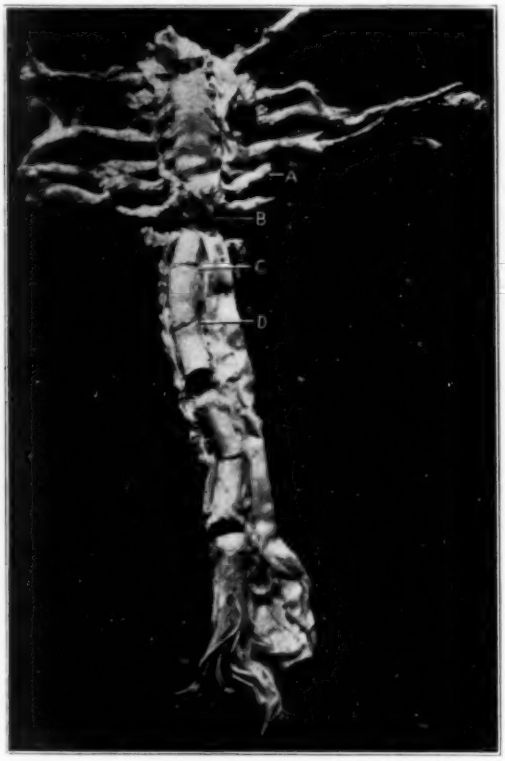

Fig. 2.—The spinal cord. *A* indicates the right eighth cervical nerve; *B*, the cord and meninges fused into an inseparable mass, and *C* and *D*, incisions made to allow for hardening.

No sweating was ever noted in connection with the mass reflexes.

After two weeks in the hospital, the child died with an unexplained hyperpyrexia.

Autopsy.—Diffuse bronchopneumonia was the immediate cause of death.

The spinal cord showed a diagonal lesion, the upper border of which extended from just above the eighth cervical root on the right to the second thoracic nerve root on the left. Above this, the spinal cord seemed firm and of normal consistency and configuration. At the upper margin of the lesion the meninges and cord became fused into an inseparable mass, which was relatively very thin from front to back and readily transmitted daylight. No vestige of cord could be identified until

the level of the fourth or fifth thoracic segment, where it began quite suddenly again as a firm, rounded, cigar-shaped structure. Below this level the cord and meninges seemed normal.

Microscopic sections were made from the midcervical region above the lesion, and from the middle and lower thoracic and lumbar regions below the lesion. The sections were stained by the Weigert method.

Sections of the cervical region showed practically complete loss of myelin in the medial half of both posterior columns (the tracts of Goll). There were still, however, a few scattered myelinated fibers throughout this region. Their size and the intensity with which they took the stain varied markedly, but most of them were relatively small. The lateral halves of the posterior columns (tracts of Burdach) were well myelinated. The fibers here varied much more in size than did the few survivors of the medial halves, and the majority of them were much larger in diameter.

In the posterior cornua of the gray matter the fibers of entry of the posterior nerve roots were seen to be intensely stained; in fact, the myelin was heavier here than in any other part of the section.

Fig. 3.—Sections from a transected cord (*A*, *B*, *C* and *D*) and from a normal cord of the same age (*E*, *F* and *G*): *A*, section at about the level of the fourth cervical nerve (transection at level of eighth cervical nerve), showing degeneration of the spinocerebellar tracts and the medial portion of the posterior columns. *B* and *C*, sections of the upper and lower thoracic cord, respectively, showing obvious degeneration in the direct and indirect corticospinal tracts and marked loss of myelin scattered through the anterior portions of the lateral columns. *D*, section of the midlumbar region of the spinal cord, showing marked degeneration of the corticospinal tracts and slighter evidence of degeneration in the anterior portions of the lateral columns. *E*, section at about the level of the fourth cervical nerve, showing normal spinocerebellar tracts and posterior columns and the large, lightly myelinated area in the lateral columns. *F*, section of the midthoracic region, showing the relative increase in the size of the lightly myelinated region of the lateral columns. *G*, section of the lower lumbar region, showing the marked diminution in the size of the lightly myelinated area of the lateral columns.

The bulk of the lateral and anterior columns stained, but with obviously less intensity than did the lateral halves of the posterior columns. There was, however, at the extreme periphery of the lateral fields, a thin margin of complete demyelinization. The white matter in close contact with the gray was a little more deeply stained than that in the middle zone of the lateral fields and the periphery of the anterior columns. The emerging fibers of the anterior nerve roots were moderately stained.

Above the transverse lesion there was thus practically complete degeneration of the myelin of the medial half of the posterior columns (the tracts of Goll) and of the spinocerebellar tracts. The rather light staining of the lateral and anterior columns remains to be explained.

A section from below the lesion in the midthoracic region showed an entirely different pattern. The posterior columns were intensely stained throughout, and the periphery of the lateral and anterior columns was also intensely stained. The posterior fields of the lateral columns, bounded by the intensely stained periphery of the column externally and the posterior horns of the gray matter medially, and fading off indefinitely anteriorly, were practically devoid of myelin, the few remaining myelinated fibers being very fine. This area of degeneration was much larger on the right than on the left. Extending anteriorly from it were smaller patches of degeneration, occupying the central portion of the lateral columns and continuing into the anterior columns. The medial portion of the anterior columns, except for a narrow margin along the anterior median fissure, also showed complete degeneration of the myelin. This area of degeneration was also unequal on the two sides, the larger portion being on the same side as the larger degeneration in the posterolateral region.

Sections lower in the thoracic and in the lumbar region showed progressively less degeneration. The large demyelinated areas in the posterolateral fields were readily demonstrable, but were smaller, while the smaller areas of degeneration in front of them were almost impossible to identify. In the lumbar region no degeneration was demonstrable in the anterior columns, but the posterolateral fields showed marked degeneration.

Below the lesion, therefore, the most striking degeneration was that of the corticospinal tracts, while extending anteriorly from them were smaller, less well defined areas of degeneration, corresponding to groups of fibers of the other long efferent tracts.

A NORMAL CORD

Failure to find in the literature any description of a normal spinal cord of this age made it necessary to study such a cord. Accordingly, the spinal cord of a baby, aged 4 months, who had died of bronchopneumonia, was secured, and sections were made of the cervical enlargement and the upper dorsal, lower dorsal and lower lumbar regions, and stained by the Weigert method. No attempt will be made to describe the sections in detail, but the differences between them and the adult normal cord will be briefly indicated. Except for their smaller size, no important difference in contour or in distribution of gray and white matter was noted. In contrast to the even staining of the white matter of the adult cord, the infantile cord showed marked variation from one fiber system to another.

Sections through the cervical enlargement showed the most intense staining in the fibers of entrance of the posterior nerve roots; next in intensity were the posterior columns, which stained evenly and darkly. The lateral columns showed marked variations in staining. At the periphery there was an intensely stained band, most clearly defined at the posterior part of the columns and fading out as it came in front of the anterior horns of the gray matter. Inside this dark band was

a large comma-shaped area with its convexity outward and its larger end posterior, which was stained much more lightly than the rest of the section. This area occupied the bulk of the lateral columns and its point extended into the anterior columns at their periphery. The white matter in immediate contact with the gray, from about the middle of the outer edge of the posterior horns and continuing anteriorly to surround the anterior horns, was stained more deeply than that of the middle zone of the lateral columns. The anterior columns, except for the tip of the lightly stained area already described, stained deeply and evenly. The fibers of the anterior nerve roots stained deeply, but not so markedly as did those of the posterior roots.

The thoracic section showed certain modifications of the cervical pattern. The posterior columns still stained darkly and evenly, as they did throughout all the sections. The dark zone at the periphery of the lateral columns was much less conspicuous and did not extend as far forward or backward as it did in the higher section. The dark zone surrounding the gray matter of the anterior horns was also much less conspicuous; it began only at the anterior half of the lateral aspect of the anterior horn and continued around the anterior horn to occupy the entire anterior column. The large, pale area, while smaller than in the cervical region, occupied practically all of the lateral columns.

In the lower thoracic region the distribution of the stain was about the same as in the upper thoracic region. The peripheral band of the lateral columns was restricted to about the middle half of the margin of the lateral columns, and the dark zone about the anterior horns had nearly disappeared, the anterior columns being very thin in this region.

The lower lumbar sections showed no dark periphery to the lateral columns, practically all of these much shrunken columns staining lightly. The anterior columns, which had increased greatly in size as compared to those of the thoracic region, stained heavily and evenly.

It would therefore appear that at 4 months of age the afferent fibers that are assembled into compact groups—the spinocerebellar tracts, the posterior columns and the posterior nerve roots—are most intensely stained. The regions occupied mostly by efferent tracts, such as the corticospinal, rubrospinal and tectospinal tracts, stain relatively lightly; the anterior nerve roots and ground bundles fall in between. The corticospinal tracts appear to have by far the least well developed myelin. In the specimen examined there was no lightly stained area corresponding to the uncrossed corticospinal tracts. This was probably due to their absence or their small size in this particular child, as both Flechsig [8] (in the new-born) and Bok [9] (in an infant aged 6 months) found the staining reactions of the direct corticospinal tract to be the same as those of the crossed corticospinal tracts.

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8. Flechsig, P.: Die Leitungsbahnen im Gehirn und Rückenmark, Leipzig, Wilhelm Engelmann, 1876.

9. Bok, S. T., in von Möllendorf, Wilhelm: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4.

SUMMARY

1. A case is described of transverse myelitis of the lower cervical cord due to obstetric trauma, in an infant who lived four months, i. e., long enough to show degeneration of the cord by the Weigert staining method.

2. Attention is called to the extensive and complex reflex activities carried on through the isolated lower segment of the cord.

3. The pathologic condition of the cord is described, and is compared with the histology of the normal cord of an infant of the same age.

CHRONIC PROGRESSIVE VASCULAR SUBCORTICAL ENCEPHALOPATHY

CHRONIC PROGRESSIVE SUBCORTICAL ENCEPHALITIS OF BINSWANGER *

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In 1894, Binswanger [1] introduced the term chronic progressive subcortical encephalitis to designate a noninflammatory disease, an uncommon form of cerebral arteriosclerosis, in which atrophy of the white matter and an intact gray matter of the cerebral hemispheres were the striking distinguishing anatomic features. Soon afterward, Alzheimer [2] substantiated the observations of Binswanger and amplified them with his own. He, also, reached the conclusion that the disease is an unique and outspoken form of arteriosclerosis, in which the deep medullary vessels are mainly affected, and hence the deep subcortical layers are subjected to the degenerative process. Because of the locally selective character of the lesion, Alzheimer was almost tempted to consider it as a form of system disease of the brain.

In the typical instance, according to both Binswanger and Alzheimer, the gray matter is usually intact, showing only in the rare case slight alterations in organization and cell structure. It is said that, even with the subcortex entirely lost or undergoing profound disintegration, the cortex may show only mild alterations. In the white matter, the arcuate fibers are as a rule undisturbed, while the deeper subcortical layers are in various stages of disintegration. The latter may be totally lost, markedly atrophied, owing to advanced degeneration, or in the process of active dissolution. The latter may take the form of circumscribed patches, which vary in number, size and distribution. They are often sharply

* Submitted for publication, June 11, 1931.

* Read at the Fifty-Seventh Annual Meeting of the American Neurological Association, Boston, May 27, 1931.

1. Binswanger, O.: Die Abgrenzung der allgemeinen progressiven Paralyse, Berl. klin. Wchnschr. **31**:1187, 1894.

2. Alzheimer: Neuere Arbeiten über die Dementia senilis und die auf atheromatöser Gefässerkrankung basierenden Gehirnkrankheiten, Monatschr. f. Psychiat. u. Neurol. **3**:101, 1898; Die Seelenstörungen auf arteriosclerotischer Grundlage, Allg. Ztschr. f. Psychiat. **59**:696 and 703, 1902.

marked off from the adjacent normal subcortex and thus simulate patches in multiple sclerosis. Then again, they are less clearly demarcated and show a gradual transition from the intact white matter at the periphery, and by way of partially altered intermediate zones pass into the completely degenerated or sclerotic center. In the diseased areas there are numerous compound granule cells and microglia filled with fat. Astrocytes are also present in sufficient numbers to give the patches the character of sclerosis. Similar observations have led Nissl [3] and, more recently, Spielmeyer [4] to regard this disease as degenerative, caused by nutritional disturbances due to arteriosclerosis of the cerebral vessels. They are not in sympathy with the term encephalitis.

In spite of the unique distribution of the lesion, its limitation to the subcortex and seat of predilection in the occipital and temporal lobes, the clinical picture does not, even in the typical case, offer safe grounds for a correct, clinico-anatomic diagnosis. The disease has no identifying features, that would distinguish it from other forms of cerebral arteriosclerosis or from other atypical instances of diffuse organic disease of the brain. It may manifest itself in the early part of the fourth decade, though the age of 50 and above is the more common period of its appearance. The onset is insidious, beginning with an impairment of memory, which is progressive and leads to profound intellectual deterioration. About the same time, the speech becomes defective; it is monotonous, monosyllabic, hesitating and occasionally dysarthric. In the course of time, vertiginous attacks, epileptiform seizures and repeated apoplectiform insults make their appearance. They may be preceded or followed by confusional or manifestly psychotic states. Somewhat later, manifestations of focal brain disease enter into the clinical picture. They include either pure motor or pure sensory aphasia, transcortical aphasia, agraphia, monoplegias, hemiplegia, visual field disturbances and disturbances in coordination of the eye movements without frank paralysis of the eye muscles. The pupils may remain normal until death, showing only in the exceptional case impaired pupillary reflexes. Psychic alterations may appear at any stage of the disease. They are often expressed in emotional instability, with explosive laughter and crying. The intellect becomes progressively dull and terminates in complete mental dilapidation. In spite of the profound intellectual defect, the patient may retain fair insight, recognizing the hopelessness of the condition. The

3. Nissl: Zur Kasuistik der arteriosklerotischen Demenz: Ein Fall von sogenannten "Encephalitis Subcorticalis," Ztschr. f. d. ges. Neurol. u. Psychiat. **19**:438, 1919-1920.

4. Quoted by Neurburger: Encephalitis subcorticalis chronica, in Bumke, Oswald: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1931, vol. 11, pt. 7. Spielmeyer, W.: Die Anatomie der Psychosen, Berlin, Julius Springer, 1930, p. 610.

disease runs a chronic and slowly progressive course, with moderate oscillations in the clinical picture. Some of the symptoms may disappear partially or become intensified at some stage of the illness. The disease may extend over a period of years, but in rare instances may terminate fatally in several months.

The case herein reported shows anatomic features typical of the disease. It shows, however, many departures from the common clinical picture. Because of the latter and since the recent literature does not contain many examples of the disease, the case is reported.

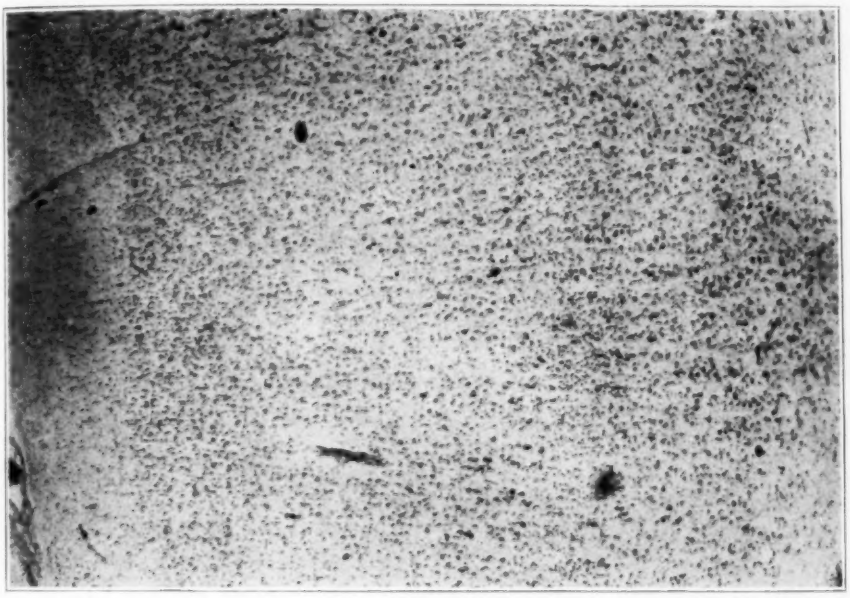

Fig. 1.—Section of the cortex, showing full preservation of the cyto-architecture and the integrity of the cellular elements. Toluidine blue stain; × 56.

REPORT OF CASE

History.—B. B., a woman, aged 40, whose past history presented no facts bearing on the fatal illness, had had no diseases of infancy, no venereal infections and no serious or disabling illnesses. She had been married twice, had had one child, who was living and well, by the first marriage and two miscarriages by the second marriage. In December, 1929, she fell and struck her back, with resultant pain in the lower part; on the next day she fell again. Since then she had continued to complain of intense pain in the back and "nervousness." She had been apparently losing ground; since about the middle of November, 1930 (about eleven months after the fall), she had been no longer able to walk, had developed urinary difficulties (frequency) and had complained of loss of sensation in the legs. She was then admitted to the Providence City Hospital.

Examination.—The patient was poorly nourished and underweight. She lay in an awkward and cramped position on the side, with the forearms flexed on the

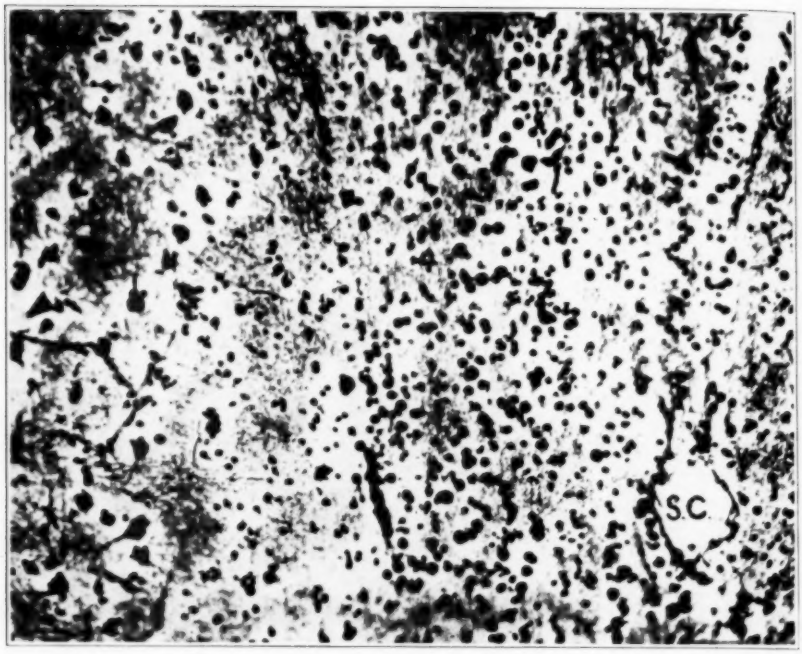

Fig. 2.—Section illustrating part of the intact cortex contrasted with marked glial infiltration of the subcortex (*S.C.*). Globus modification of Hortega silver carbonate stain; × 170.

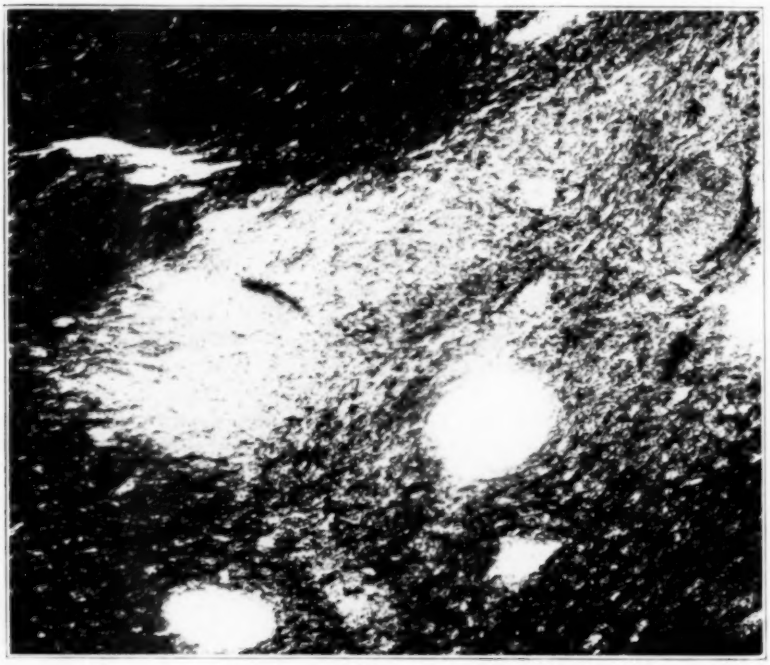

Fig. 3.—Circumscribed area of demyelinization in the subcortex. Spielmeyer myelin stain; × 56.

upper arms and the legs drawn up on the abdomen. There was considerable general muscular rigidity, not unlike that seen in decerebrate rigidity. The pupils reacted to light and in accommodation. The deep reflexes were exaggerated; the abdominal reflexes were absent. There was a Babinski sign and a sustained ankle clonus on the right. The jaw jerk was exaggerated. The masseter muscles were apparently in a state of tetanic contraction, and an attempt to open the mouth was unsuccessful, although occasionally, when other muscular movements were provoked, the mouth would open involuntarily for a short excursion. There was a positive Chvostek sign. Wassermann tests of the blood gave negative reactions. The cerebrospinal fluid contained 10 cells and gave a doubtful Wassermann reaction but a negative colloidal gold curve.

Fig. 4.—Transitional zone between the relatively intact myelin structure and the demyelinizing center of a patch. Spielmeyer myelin stain; × 170.

Course.—The diagnosis in this case was difficult. The symptoms were too generalized to be accounted for by a circumscribed lesion. The character of the disease process could not be identified in the early stage of the clinical course.

The patient's condition declined rapidly. She assumed a more pronounced decerebrate posture. She became rigid, with flexion of the thighs on the abdomen, extension of the feet, flexion of the arms and wrists and hyperextension of the head. Bilateral pyramidal tract signs developed, with hyperreflexia and bilateral Babinski and Hoffmann signs. The jaw became fixed. The rigidity, however, intense as it was, was not constant and would alternate with periods of relaxation. Her mentality was clouded; she was confused and disoriented. At this time arterial disease in the midbrain, because of the manifestations of decerebrate rigidity, was considered by one of us (Dr. Farnell). Lobar pneumonia developed, and death ensued eight weeks after admission to the hospital.

Necropsy.[5]—Gross Anatomy: The body was that of a poorly nourished white woman. The pupils were unequal, the right measuring 6 mm. and the left 5 mm. The heart was soft and flabby. The valves appeared normal. The aorta showed very marked thickening of the intima in longitudinal ridges, not unlike that seen in syphilis. The coronary arteries showed some plaques in the lining wall, but there were apparently no occlusions. In the center of the upper lobe of the right lung was an area of consolidation. The left lung showed in the lower lobe a

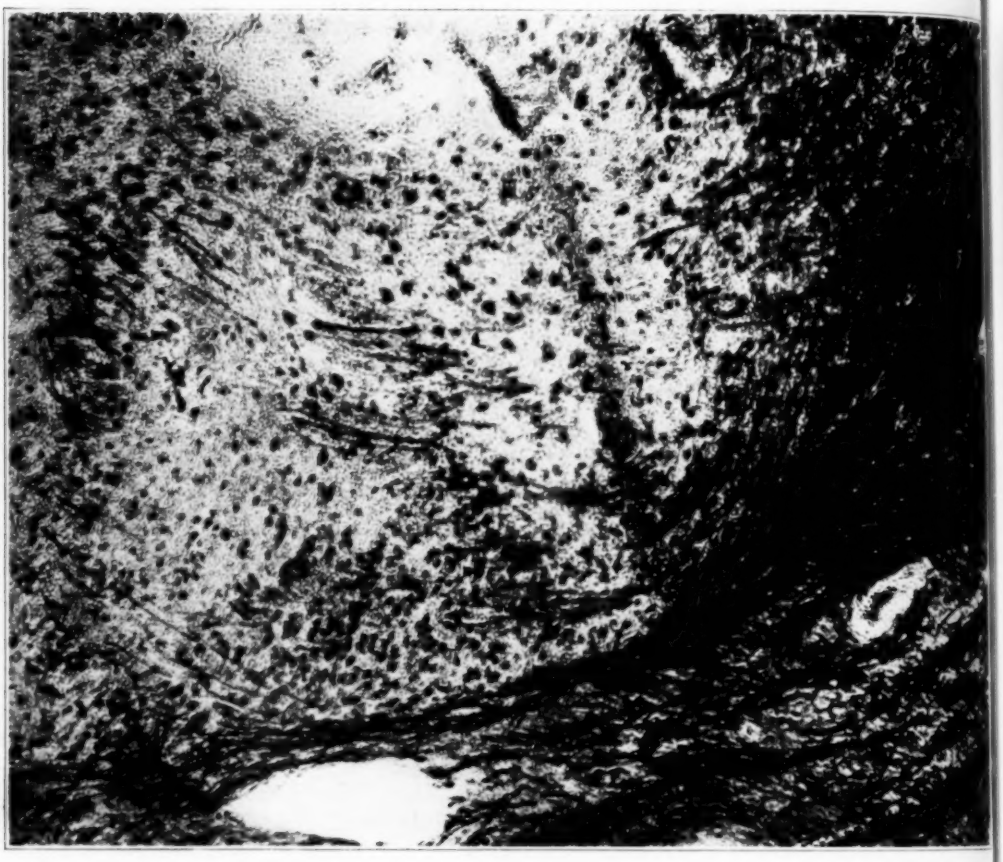

Fig. 5.—Demyelinizing area, showing aggregation of compound granular cells and fragments of myelin fibers. Spielmeyer myelin stain; × 70.

pneumonic process. There was also an extensive area of fibrosis in this region. The spleen was soft and mushy. The gastro-intestinal tract showed nothing abnormal. The liver was soft and small. Both kidneys were small and showed the characteristic appearance of chronic vascular disease. The uterus had multiple fibroids.

5. For the gross anatomic description we are indebted to Dr. H. L. Smiley, Providence, R. I.

The brain weighed 1,225 Gm. It was firm and heavy with a leathery resistance on cutting. The vessels at the base of the brain showed definite arteriosclerosis. The cortex was of normal width, but the subcortex was narrow and of unusual hardness.

Microscopic Anatomy: Cerebral cortex. The gray matter of the cerebral hemisphere was found intact (fig. 1). There were no apparent reduction in cells and no outspoken degeneration of nerve cells, although they appeared to contain a somewhat larger amount of fat when stained with the Herxheimer scarlet red

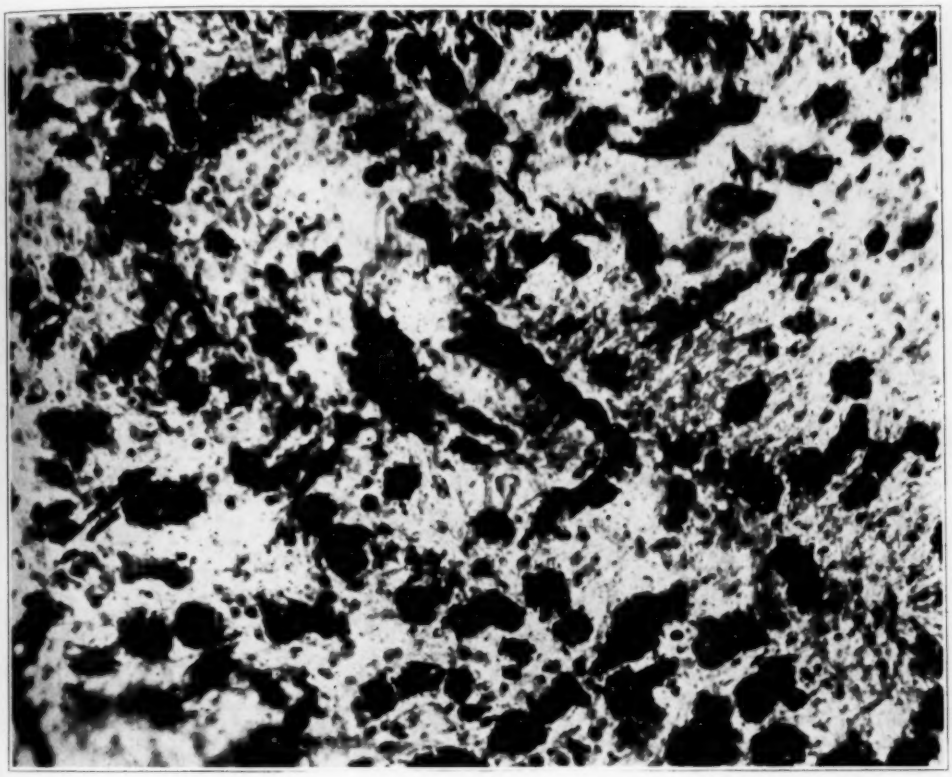

Fig. 6.—Subcortex, showing a large aggregation of compound granular cells filled with fat about a disorganized blood vessel. Herxheimer scarlet red stain; × 310.

method. There was no increase in glial elements, and the vessels showed no decided changes.

Cerebral subcortex. The subcortex, in striking contrast to the cortex, showed profound structural alterations. It was markedly reduced in width, and with a low magnification dense masses of glia nuclei could be seen (fig. 2). By means of the Weigert-Spielmeyer myelin stains, great reduction and irregularities in its staining affinity were disclosed. In some parts there were large zones of total demyelinization; in other parts, smaller, somewhat irregular, bald spots (fig. 3), indicating a total loss of myelinated material in circumscribed areas. Such areas often simu-

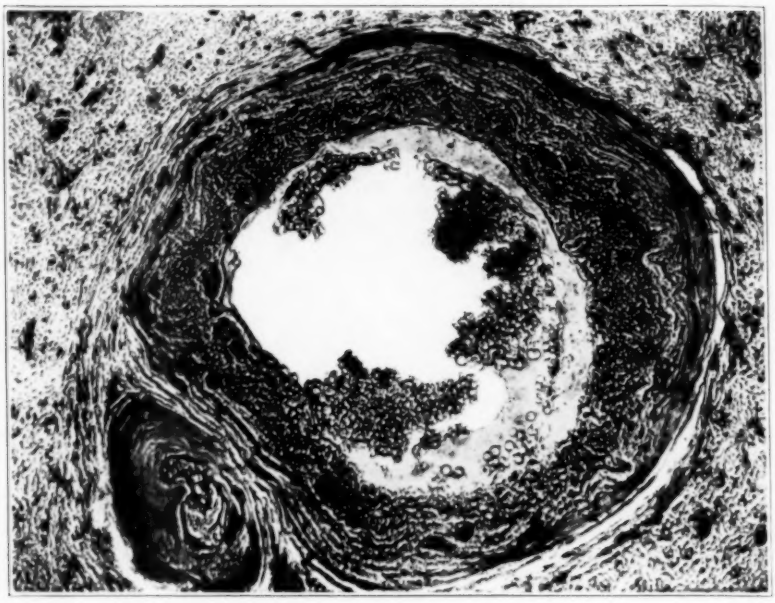

Fig. 7.—Large medullary blood vessel, showing advanced arteriosclerosis. Herxheimer scarlet red and hematoxylin; × 120.

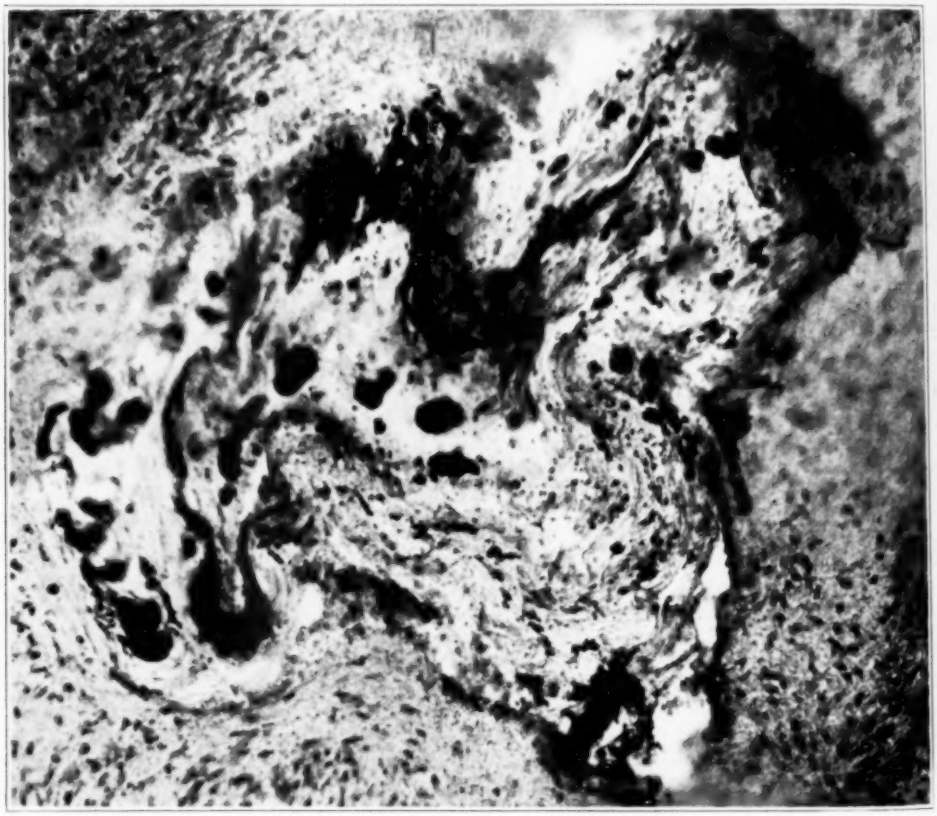

Fig. 8.—Blood vessels in the sclerotic area, showing complete disorganization of the vessel wall with almost total occlusion of the lumen. Globus modification of the Hortega silver carbonate stain, counterstained with Herxheimer scarlet red; × 420.

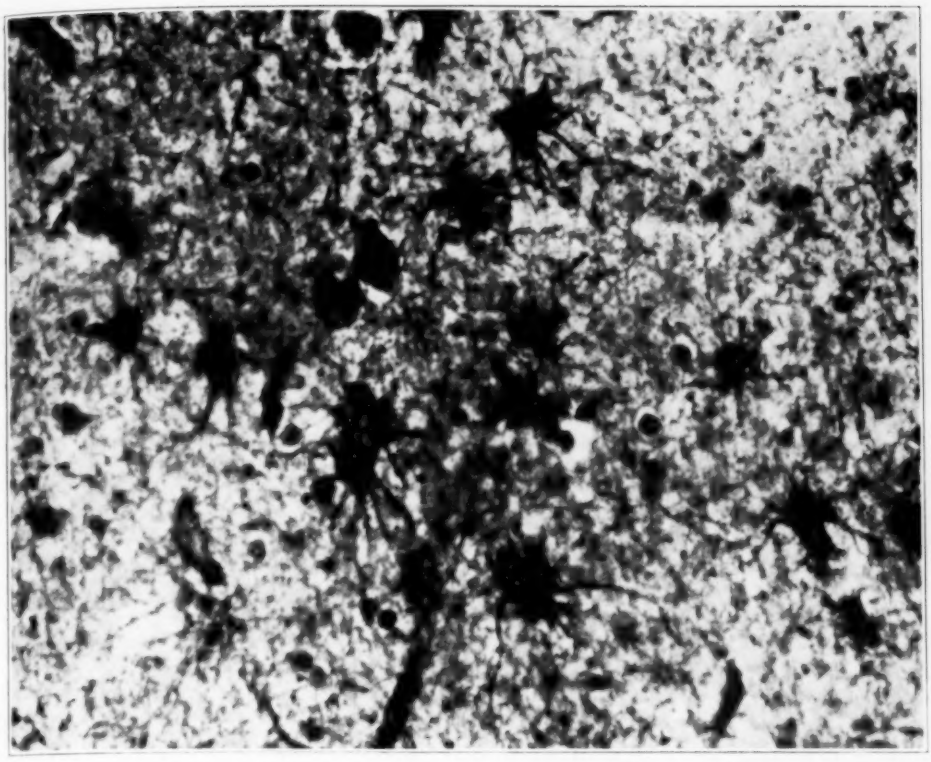

Fig. 9.—Large astrocytes in a sclerotic patch. Globus modification of the Cajal gold sublimate stain; × 460.

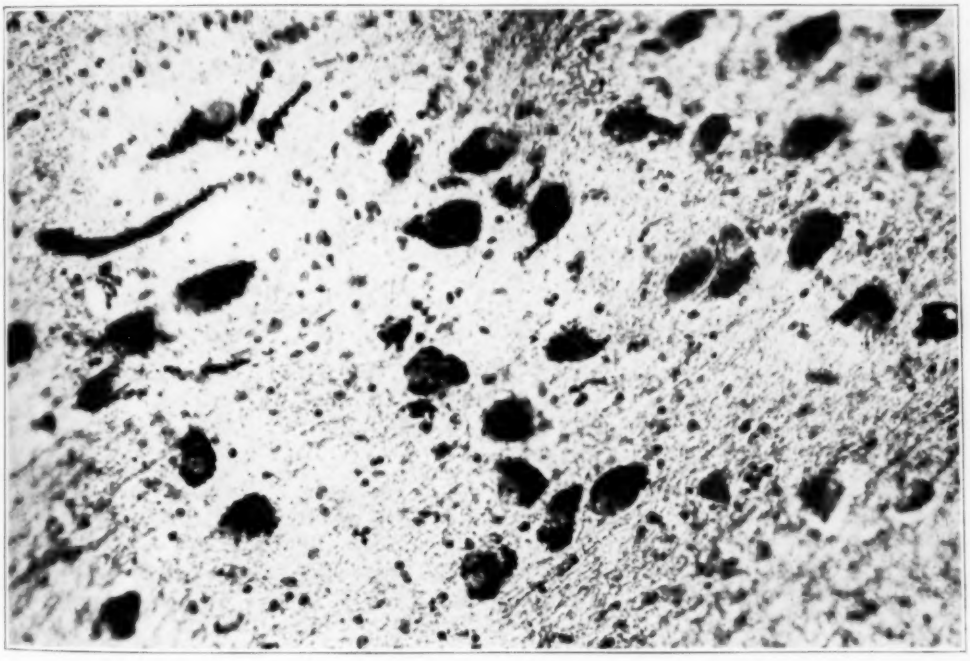

Fig. 10.—Substantia nigra, showing intense infiltration of nerve cells with fat. Herxheimer scarlet red stain and hematoxylin; × 240.

lated those noted in multiple sclerosis, and under a higher magnification, in Bielschowsky preparations, there were seen many fine naked axis cylinders running through the fully demyelinated patch. Again, areas in which a transition from the well preserved periphery to the demyelinated centers could be demonstrated (fig. 4). In many of these patches large numbers of compound granular cells and fragments of myelin (fig. 5) were found, indicating a still active process of demyelinization. With the fat stains, large accumulations of compound granular cells and microglia, which were filled with fat, could be demonstrated in almost every demyelinizing patch. They grouped themselves mainly about blood vessels (fig. 6); however, not to the full exclusion of extravascular territory. In the midst of such areas

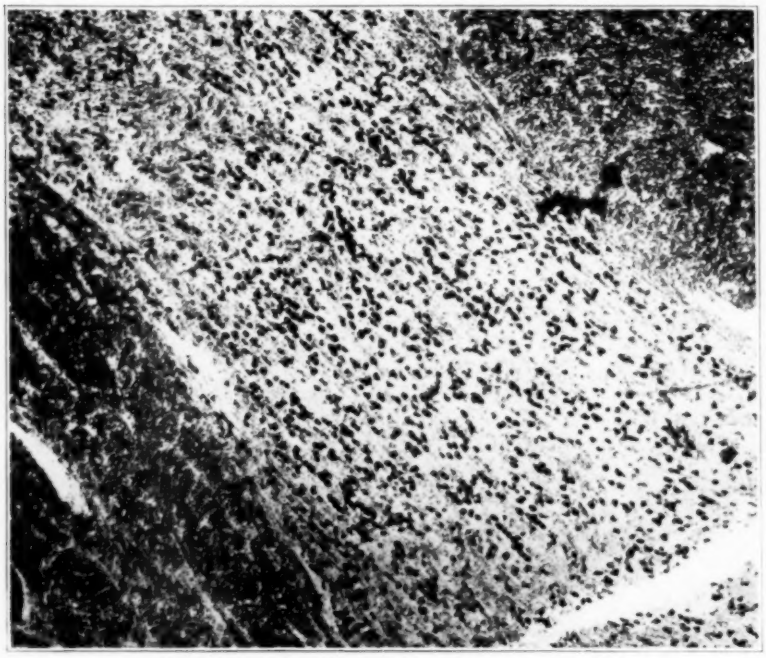

Fig. 11.—Section of the medulla oblongata, showing pyramidal tract undergoing secondary degeneration. The path of the tract is indicated by a large accumulation of compound granular cells filled with fat. Herxheimer scarlet red stain; × 50.

blood vessels were found which showed varying degrees of degeneration, from advanced arteriosclerotic alterations (fig. 7) to the most profound general disintegration (fig. 8). At the periphery of such zones a sclerosing process with large aggregations of astrocytes was in progress (fig. 9).

The degenerative changes, however, were not limited to the myelinated structure in the cerebral subcortex. Nerve cells in the basal ganglia and in the substantia nigra (fig. 10) showed well marked fatty infiltrations, which were definitely pathologic. In the brain stem, the pyramidal tracts showed similar degenerative alterations throughout their extent (fig. 11).

COMMENT

It is obvious from the anatomic observations in our case that the disease was degenerative, and that it was very likely caused by changes in the vessels nourishing the involved parts of the brain. For the present, we have no better explanation for the selective character of the disease than that the longer subcortical vessels (Alzheimer), having undergone arteriosclerosis, caused nutritional disturbances in the deeper layers in the white matter of the cerebral hemispheres, thereby limiting the disease to the subcortex.

The clinico-anatomic diagnosis during life is beset with great difficulty. The clinical picture in this disease, as verified by necropsy, is in keeping with the anatomic alterations. In our case a diffuse widespread disease process, implicating the basal ganglia, the substantia nigra and the pyramidal tracts, is in full accord with the objective neurologic signs disclosed by our patient.

In many ways this disease shows great similarity to the so-called Schilder's disease,[6] or the progressive subcortical degenerative encephalopathy of Globus and Strauss,[7] in which the subcortex is the seat of a disease process, and the occipital and temporal lobes are sites of predilection. In the latter no arteriosclerotic vessel changes are found, and the disease occurs commonly in the young, although Stewart, Greenfield and Blandy [8] reported a case in a patient 43 years of age.

Despite the apparent similarity in the location and the degenerative character of the disease process, its occurrence in divergent clinical types would seem to point to the probability that different causative factors are operative in the production of the somewhat similar anatomic pictures.

SUMMARY AND CONCLUSIONS

A case of Binswanger's chronic progressive encephalitis is described. It differs from the typical case in that it occurred in a somewhat younger person, ran a rather rapid clinical course and manifested decerebrate rigidity as a striking atypical feature. The latter may find explanation in the degenerative changes noted in the substantia nigra.

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6. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose (über Encephalitis periaxialis diffusa), Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912; Zur Frage der Encephalitis periaxialis diffusa (sogenannte diffuse Sklerose), ibid. **15**: 359, 1913.

7. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy (Schilder's Disease), Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

8. Stewart, T. G.; Greenfield, J. G., and Blandy, M. A.: Encephalitis Periaxialis Diffusa: Report of Three Cases with Pathological Examination, Brain **50**:1, 1927.

The disease is degenerative; Binswanger, though recognizing it as such, erred in choosing the term encephalitis. Instead the term chronic progressive vascular subcortical encephalopathy is suggested as more descriptive of the lesion and of its possible etiology. The disease presents no clearly distinguishable clinical diagnostic features, but merits consideration in the differential diagnosis of atypical instances of cerebral arteriosclerosis.

HISTOLOGIC CHANGES IN THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

III. REACTION OF MICROGLIA AND OLIGODENDROGLIA *

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AND
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LOS ANGELES

It has been our purpose to study the finer microscopic changes that take place in the various cellular elements of the brain in cases of fatal injury of the head. Many descriptions have been given of gross changes in such cases, usually under the general appellations of concussion, contusion, hemorrhage and "wet brain." In such reports, occasional references have been made to the microscopic changes. In previous communications a general survey of the field was first outlined,[1] and later a more detailed investigation was made concerning the changes in the choroid plexus and ependyma.[2]

The introduction of the newer metallic methods by Cajal and his co-workers opened a new field for investigation of the supporting elements of the central nervous system. These methods have already been utilized in the study of brain injury in experimental animals. So far as we know, such investigations have not been conducted on human material. It is our purpose at this time to submit a critical study of the changes occurring in microglia and oligodendroglia in selected cases of fatal injury to the brain and to attempt an explanation of the rôle that such changes may play in the clinical and pathologic picture. The effect of injury on the neuroglial and neuronal elements will be considered in later communications.

REVIEW OF THE LITERATURE

The history of the neuroglia begins with the fundamental studies of Virchow,[3] who differentiated a supporting ground substance from

* Submitted for publication, May 26, 1931.

* The drawings in this article were made by Dr. Courville.

* From the Neurological Service and the Neuropathological Laboratory of the Los Angeles County General Hospital.

1. Rand, Carl W.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: I. A Preliminary Report, Arch. Surg. **22**:738 (May) 1931.

2. Rand, Carl W., and Courville, Cyril B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: II. Choroid Plexus and Ependyma, Arch. Surg. **23**:357 (Sept.) 1931.

3. Virchow, R.: Ueber das granulierte Ansehen der Wandungen der Gehirnventrikel, Allg. Ztschr. f. Psychiat. **3**:242, 1846.

the functional neuronic elements. His teased preparations clearly showed the typical neuroglia, but it is doubtful whether he ever distinguished the cells under consideration in this study. It was not until the silver method introduced by Golgi [4] that the definite histologic characteristics of the neuroglia were appreciated. Golgi succeeded in separating the fibrous and the protoplasmic forms, designating them as "spider" and "mossy" cells. Weigert [5] demonstrated the neuroglia fibrillae by a new staining method, but it is questionable whether he appreciated the existence of cells other than the classic astrocytes.

Although their relationship to other interstitial elements was not fully understood for many years, the conception of the microglia was historically introduced by the embryologic studies of Eichhorst [6] and His.[7] They expressed the belief that certain elements that they observed invading the ectodermal tissues of the fetal central nervous system were of mesodermal origin. His stated the further belief that these mesodermal elements formed some of the true neuroglia.

Perhaps the earliest observers to note that the structure of some of the nerve elements could not be demonstrated by existing methods were Capobianco and Fragnito.[8] Contrary to the belief of His, they held that these "adendritic cells" were of mesodermal origin and were probably not true neuroglia. Schaper [9] also described these "naked nuclei," but had little to suggest as to their possible function, believing that they remained as "indifferent" undeveloped cells. It remained for Ford-Robertson [10] to devise an impregnation method, which, according to his illustrations, was capable of demonstrating both microglia and oligodendroglia. These elements he believed to be of mesodermal origin and grouped them collectively under the term of "mesoglia." Save for the casual reference of Cerletti,[11] unfortunately the work of Ford-Rob-

4. Golgi, C.: Sulla fina anatomia della sistemo nervoso, Milan, Ulrico Hoepli, 1886.

5. Weigert, Carl: Beiträge zur Kenntnis der normalen menschlichen Neuroglia, Frankfurt, A. Weisbrod, 1895.

6. Eichhorst, H.: Ueber die Entwicklung des menschlichen Rueckenmarks und seiner Formelemente, Virchows Arch. f. path. Anat. **64**:425, 1875.

7. His, W.: Histogenes und Zusammenhang der Nervenelemente, Arch. f. Anat. u. Entwcklngsgesch. (Anat. Sect.), 1890, vol. 95.

8. Capobianco, A., and Fragnito, O.: Nuove cicerche sulla genesi e i rapporti nutritivi degli elementi nervosi e nevroglia, Ann. di nevrol. **16**:81, 1898.

9. Schaper, A.: Die frühesten Differenzierungsvorgänge im Centralnervensystems, Arch. f. Entwcklngsmechn. **5**:81, 1897.

10. Ford-Robertson, W.: A Microscopic Demonstration of the Normal and the Pathological Histology of Mesoglia Cells, J. Ment. Sc. **46**:724, 1900.

11. Cerletti, U.: Studi recenti sull' istogenesi della nevroglia, Ann. d. Ist. psichiat. d. r. Univ. di Roma, 1908, vol. 6.

ertson was given scant attention until del Rio Hortega [12] brought it again into prominence.

Meanwhile, these adendritic elements had been noted and described by many others. With his method for tigroid substance, Nissl [13] demonstrated the presence of "Stäbchenzellen," elongated rod-shaped cells in which the nuclei were surrounded by a narrow zone of cytoplasm. Hardesty [14] described "signet ring" forms in the developing central nervous system, which appeared about the time of myelinization, and which he believed had something to do with this process. He was evidently describing interfascicular oligodendroglia. In the absence of more definite conceptions as to their structure, it was natural that peculiar notions should develop as to their function. One group of investigators held that such cells were "germinal glia" which developed into adult neuroglia when the conditions demanded. Another group considered them to be another type of adult neuroglia, even though their structure had not been clearly demonstrated. Elaborating on the first conception, Bonome [15] considered them to be the starting point for gliomas, designating them as "cellule gliogenetiche." Achúcarro [16] called them "interstitial elements," and Cajal [17] grouped together all the adendritic corpuscles under the term "third element." Del Rio Hortega [18] repeated the work of Ford-Robertson and finally, with a new method of silver carbonate impregnation, succeeded in subdividing this group into two cell types, the microglia [12] and the oligodendroglia.[19]

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12. del Rio Hortega, P.: El "tercer elemento" de los centros nerviosos: I. La microglia en estado normal; II. Intervención de la microglia en los procesos patológicos; III. Naturaleza probable de la microglia, Bol. Soc. españ. de biol. **9**:69, 1919.

13. Nissl, F.: Zur Histopathologie der paralytischen Rinderkrankung, Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1904, vol. 1, p. 315.

14. Hardesty, Irving: On the Development and Nature of the Neuroglia, Am. J. Anat. **3**:229, 1904.

15. Bonome, A.: Nuove osservazioni sulla struttura ed istogenesi dei gliomi, Atti d. r. Ist. Veneto di sc., lett. ed arti **57**:1011, 1908.

16. Achúcarro, N.: Neuroglia y elementos intersticiales patológicos del cerebro, impregnados por los métodos de reducción de la plata o por sus modificasiones, Trab. d. lab. de invest. biol. Univ. de Madrid **9**:161, 1911.

17. Ramón y Cajal, S.: Contribución al conoscimiento de la neuroglia del cerebro humano, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:254, 1913.

18. del Rio Hortega, P.: Noticia de un nueva y fácil métado para la coloración de la neuroglia y del tejido conjunctivo, Trab. d. lab. de invest. biol. Univ. de Madrid **15**:367, 1918.

19. del Rio Hortega, P.: Estudios sobre la neuroglia: La glia de escasas radiciones (oligodendroglia), Bol. r. Soc. españ. de hist. nat., 1921, vol. 10.

CHANGES IN MICROGLIA AND OLIGODENDROGLIA IN EXPERIMENTAL BRAIN INJURIES

The reaction of the microglia and the oligodendroglia to various lesions of the brain has been made the subject of many contributions during the past few years. Our present interest in the subject, however, concerns itself principally with changes that have been described as a result of experimental brain wounds.

Microglia.—The first clearcut descriptions of normal and abnormal forms of microglia were given by del Rio Hortega.[20] He demonstrated all the transitional forms from the normal cell to the development of compound granular corpuscles. It is evident from the results of various investigations that these changes are practically identical in abscesses (Penfield[21]), softening (Globus[22]) and regressive changes in gliomas (Penfield[23]), as well as in brain injury. In other words, there is a particular response of a specific cell to a destructive process in the central nervous system, regardless of the etiologic factor producing it. Cone[24] has described the changes occurring in microglia in acute poliomyelitis, and cerebrospinal meningitis. These are practically the same as those found in experimental injury. From the latter standpoint, del Rio Hortega[25] was the first to describe such changes in injury. His first observations have been confirmed by Penfield,[26] and Hortega and Penfield.[27] Alberca[28] studied the changes in microglia following experimental wounds in the cords of rabbits. Penfield gave the impression that the first essential change in microglia in response to injury is the formation of rod cells (Stäbchenzellen). This consists of an

20. del Rio Hortega, P.: Estudio sobre la neuroglia: La microglia y su transformación en células en bastoncito y cuerpos granulo-adiposos, Trab. d. lab. de invest. biol. Univ. de Madrid **18**:37, 1920.

21. Penfield, Wilder: Brain Abscess, in Nelson: Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 2, p. 311.

22. Globus, Joseph H.: Glial Response in Chronic Vascular Disease of the Brain, Arch. Neurol. & Psychiat. **20**:14 (July) 1928.

23. Penfield, Wilder: Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77, 1925.

24. Cone, William: Acute Pathologic Changes in Neuroglia and Microglia, Arch. Neurol. & Psychiat. **20**:34 (July) 1928.

25. del Rio Hortega, P.: Poder fagocitario y movilidad de la microglia, Bol. Soc. españ. de biol. **9**:154, 1919.

26. Penfield, Wilder: Phagocytic Activity of Microglia in the Central Nervous System, Proc. New York Path. Soc. **25**:71, 1925.

27. del Rio Hortega, P., and Penfield, W.: Cerebral Cicatrix: The Reaction of Neuroglia and Microglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**:278, 1927.

28. Alberca, R.: Intervención precoz de la microglia en las heridas experimentales de la medula del conejo, Bol. Soc. españ. de biol. **11**:81, 1926.

elongation of the nucleus with moderate swelling of the cytoplasm of the polar processes. Transitional forms up to compound granular corpuscles have been seen as early as the first day after an aseptic stab wound. Examination of older wounds shows all transitions from the normal after the second day. These transitional forms may be found until the process of carrying away destroyed tissue has been completed. Farrar [29] described macrophages filled with fat as early as eighteen hours after experimental injury of the brain. It seems evident from these observations that the microglia cells react promptly, for even fully developed compound granular corpuscles may be found within a few hours of the production of the lesion.

Oligodendroglia.—It is evident from the observations of various observers that the reaction of oligodendroglia to injurious processes of one sort or another differs considerably from that of microglia. This was to be anticipated from the rediscovery of this element by del Rio Hortega,[25] who found it to differ in origin and structure from the microglia. Penfield [30] confirmed the observations of del Rio Hortega and suggested their relation to the formation of myelin. Penfield and Cone [31] demonstrated a change in the oligodendroglia characterized by hypertrophy of the cytoplasm and followed by swelling and vacuolization of the cell body which they termed "acute swelling of the oligondendroglia." These changes were found in tuberculous meningitis, malnutrition, anterior poliomyelitis and in other conditions in which stupor was present before death. This condition was found in experimental animals following ligation of the common carotids. It was also present several hours after death as a progressive postmortem change. Ferraro and Davidoff [32] studied the reaction of oligodendroglia in experimental injury of the brain. They found acute swelling to be present in the cortex immediately adjacent to the lesion as early as twelve hours following injury. It was still present from twenty to forty-eight hours after injury. They found that after two days acute swelling was seldom met with, and concluded that it was an early and transitory reaction. They agreed with Penfield and Cone that acute swelling is

29. Farrar, C. B.: The Phenomena of Repair in the Cerebral Cortex, in Nissl, F.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1908, vol. 3, p. 1.

30. Penfield, Wilder: Oligodendroglia and Its Relation to Classical Neuroglia, Brain **47**:430, 1924.

31. Penfield, W., and Cone, W.: Acute Swelling of Oligodendroglia: A Specific Type of Neuroglia Change, Arch. Neurol. & Psychiat. **16**:131 (Aug.) 1926; The Acute Regressive Changes of Neuroglia (Amoeboid Glia and Acute Swelling of Oligodendroglia), J. f. Psychol. u. Neurol. **34**:204, 1926.

32. Ferraro, A., and Davidoff, L. M.: The Reaction of the Oligodendroglia to Injury of the Brain, Arch. Path. **6**:1030 (Dec.) 1928.

Case	Age	Sex	How Injured	Time Between Injury and Death	Time Between Death and Tissue Fixation	Gross Pathology	Histopathology
1	63	F	Automobile collision	45 minutes	Within 1 hour	Generalized subarachnoid hemorrhage; contusions over left temporal lobe and laceration right temporal lobe	Acute swelling of oligodendroglia; microglia show some swelling of their processes
2	29	M	Automobile collision	31 hours	4 to 5 hours	Fracture of vault and base of skull; large left temporal subarachnoid clot; left intracerebral (temporal lobe) hemorrhage	Acute swelling, fusion and clumping of oligodendroglia; microglia show early swelling of the processes; active amitotic cell division; some rod cell forms
3	41	M	Automobile collision	2 hours	3 hours	Compound, comminuted skull fracture in left frontoparietal region with laceration of both frontal lobes; extensive subarachnoid hemorrhage	Acute swelling, fusion and clumping of oligodendroglia; microglia unchanged
4	51	M	Old injury Recent injury probably struck by an automobile	7 months 51 hours	..... 3½ hours	Fracture of wing of left sphenoid bone from recent injury; local subarachnoid hemorrhage in lower right motor area; old cavity in right temporal lobe extending from surface to ventricle	Oligodendroglia show varying degrees of acute swelling; zone of connective tissue and gliosis about old cavity; all stages of microglia changes about old cavity, occurring chiefly in groups in degenerative areas
5	38	M	Automobile	6¾ hours	1½ hours	Extensive compound comminuted fracture of left vault and base of skull; left extradural hemorrhage; extensive laceration of left cerebral hemisphere; contusion of right temporal lobe; extensive subarachnoid hemorrhages; hemorrhage into pons	Active amitotic division and acute swelling of oligodendroglia; active amitotic division of microglia with early swelling of larger processes
6	26	M	Automobile collision	3 days and 19 hours	2 to 3 hours	Fracture of right side of occipital bone; left subdural hemorrhage; localized subarachnoid hemorrhages; contusion of left temporal lobe; extensive petechial hemorrhages in white substance of cerebral hemispheres	Amitotic cell division and acute swelling of oligodendroglia; active mitotic and amitotic cell divisons of microglia with all transitional forms up to fully developed compound granular corpuscles
7	14	M	Automobile collision	38 days	2 hours	Compound comminuted depressed skull fracture of left vault; old laceration of left temporoparietal region; moderate internal hydrocephalus with yellow ventricular fluid	Connective tissue and glial reaction at margin of scar; acute swelling and various regressive changes in oligodendroglia all transitional forms of microglia up to compound granular corpuscles
8	22	M	Fell from second story window to cement walk	4½ days	2 hours	Fracture of left femur and both bones of left forearm; multiple widespread petechial hemorrhages of the brain	Acute swelling of oligodendroglia; microglia show transitional forms near embolic areas up to compound granular corpuscles
9	32	M	Assaulted	14 days	4 hours	Contusion of brain in Broca's area	Amitotic division, acute swelling of oligodendroglia; active amitotic division of microglia with all transitional forms of cells; compound granular corpuscles not completely developed
10	35	M	Automobile collision	14 hours	3½ hours	Fracture of petrous portion right temporal bone; small subarachnoid hemorrhage and multiple petechial hemorrhages; multiple fractures of ribs with contusion of lungs; tear of aorta with mediastinal hemorrhage	Widespread acute swelling of oligodendroglia; microglia normal or showing early swelling
11	9	F	Fell from fire escape striking head on	26 hours	1½ hours	Extensive basal skull fracture; generalized subarachnoid hemorrhage; extensive contusion and laceration of left temporal	Acute swelling and various regressive changes of oligodendroglia; amitotic cell division of microglia; late transitional forms were found; no compound granular corpuscles

11	9	F	Fell from fire escape striking head on cement walk	26 hours	1½ hours	Extensive basal skull fracture; generalized subarachnoid hemorrhage; extensive contusion and laceration of left temporal lobe	Acute swelling and various regressive changes of oligodendroglia; amitotic cell division of microglia; late transitional forms were found; no compound granular corpuscles
12	35	M	Fell in a seizure striking head	4 days and 9 hours	6½ hours	Meningovascular syphilis; local subarachnoid hemorrhage in right parietal region; petechial hemorrhages in underlying white matter	Acute swelling of the oligodendroglia; microglia characteristic of cerebral syphilis; numerous rod cells and early transitional forms; some small vacuoles found
13	10	M	Struck by automobile	2 hours	1 hour	Basal skull fracture right occiput; contusion of base of both frontal lobes; moderate general subarachnoid hemorrhage	All stages of acute swelling of oligodendroglia; microglia show rod cells and early swelling of larger processes
14	75	F	Struck by street car	2 hours	3½ hours	Extensive basal skull fracture; laceration of right frontal lobe; extensive and marked subarachnoid hemorrhages; hemorrhage into lateral ventricles	Oligodendroglia show very minor degree of acute swelling; microglia show practically no change
15	48	M	Struck by train	Within 30 minutes	1 hour	Basal skull fracture; marked diffuse subarachnoid hemorrhage	Oligodendroglia show acute swelling; microglia are unchanged
16	67	M	Unknown	3½ days	5½ hours	Basal skull fracture; small left extradural hemorrhage; contusions of both temporal lobes; minor diffuse subarachnoid hemorrhage; multiple fractured ribs and left femur	Oligodendroglia show little evidence of acute swelling; occasional cell shows moderate swelling; a few show small vacuoles; microglia show only minor swelling of major processes near contused brain; amitotic cell division quite active
17	84	F	Struck by automobile	1¼ hours	2 hours	Basal skull fracture, moderate subarachnoid hemorrhage over the frontal lobes; contusion of tips of frontal lobes	Oligodendroglia show acute swelling; some fusion forms are found; microglia are practically unchanged
18	35	M	Automobile collision	3 days and 3 hours	1 hour	Basal skull fracture, multiple petechial hemorrhages throughout entire brain; fracture of the ribs and lobar pneumonia; meningitis	Oligodendroglia show acute swelling, binucleated forms and fusion forms; microglia practically unchanged
19	70	F	Struck by automobile	Killed outright	Within 30 minutes	Basal skull fracture, marked diffuse subarachnoid hemorrhage; multiple petechial hemorrhages; contusion of right temporal lobe; fracture of both bones of left leg	Oligodendroglia show early acute swelling; fusion forms are present; microglia unchanged
20	48	M	Fell while intoxicated	5 days	7 hours	Hemorrhage into substance of the left temporal lobe	Oligodendroglia show marked acute swelling; microglia show all transitional stages up to the formation of the compound granular corpuscles
21	17	F	Automobile accident	56 hours	10 hours	Basal skull fracture; marked left subdural hemorrhage; contusion of both temporal and right frontal lobes; hemorrhage into ventricles	Oligodendroglia show tremendous swelling in the cortex; less marked change in the white matter; microglia show early swelling in slightly bruised cortex; binucleated forms also seen
22	33	M	Automobile accident	6½ days	4½ hours	Diffuse subarachnoid hemorrhages; multiple petechial hemorrhages of cerebrum and brain stem	Oligodendroglia show acute swelling throughout all sections; microglia unchanged in undamaged cortex; transitional forms and compound granular corpuscles in bruised area
23	30 ?	M	Fell down stairs striking head on concrete	About 12 hours	9 hours	Extensive fracture of vault and base of the skull with some depression in right temporal region; extensive subarachnoid hemorrhage; contusion and laceration of the left temporal lobe; intrapontile hemorrhage	Oligodendroglia show a variable degree of swelling, particularly in the gray matter; all cells not involved to same degree; microglia show early swelling of larger processes adjacent to bruised areas; normal elsewhere
24	55	F	Struck by automobile	23½ hours	2 hours	Basal skull fracture; moderate subarachnoid hemorrhage at tips of temporal lobes	Oligodendroglia show acute swelling; fusion and binucleated forms are present; microglia show direct cell division especially in the subpial region; nuclei often vacuolated; occasional swelling of major processes; otherwise normal

a reversible reaction. In addition to acute swelling, they also described atrophic degeneration, hypertrophy, hyperplasia and the formation of compound granular corpuscles from this element. They also found that oligodendroglia tended to fuse into clusters, the nature of which reaction was not entirely clear.

SOURCE OF MATERIAL AND METHODS OF STUDY

The material used was made available through the courtesy of Drs. A. F. Wagner and John W. Schaefer of the coroner's department. Twenty-four specimens were selected from cases, most of which were studied by us either at the Los Angeles County General Hospital or in private practice. They were selected from a larger series with two points in view: (1) the length of time elapsing between injury and death and (2) the type of brain lesion. It was important to know the time interval of survival in order to trace the chronological sequence of changes occurring in the cellular elements. In this respect we followed the plan that Penfield and others employed in their studies of brain injuries in animals. We have followed this sequence in studying the various types of lesions, such as edema, contusion, laceration and hemorrhage.

In order to be of greatest value, the material in these cases should be as free as possible from postmortem change. In our series this was the case as far as existing circumstances permitted. The body was usually delivered to the coroner's department from one-half hour to two hours after death, and embalming was begun at once. Unfortunately, in five cases tissue fixation was delayed for from five to ten hours after death. In the accompanying table, the interval of time from death until injection will be found. In the majority of cases, we believe that this interval did not permit any extensive postmortem change. After autopsy the brain was immersed in a 10 per cent solution of commercial formaldehyde, where it remained until tissue fixation was complete. Suitable blocks were then taken, and frozen sections were cut, some of which were stained with hematoxylin and eosin to bring out nuclear detail as well as general tissue architecture. Other sections were stained by the scarlet red and the nile blue sulphate methods for fat. Because the tissue had been fixed in formaldehyde, we were limited to the use of Penfield's[33] combined method for the demonstration of both microglia and oligodendroglia. In every case, after one or more trials, we were successful in demonstrating more or less completely the details of both types of cells.[34] We also utilized the suggestion of Ferraro and Davidoff of counterstaining specific metallic preparations with Herxheimer's method for fat.

In this study we are concerned primarily with the reaction of microglia and oligodendroglia to specific types of brain injury as well as to generalized changes such as edema. The salient features of each case are incorporated in the table on pages 610 and 611.

33. Penfield, W.: A Method of Staining Oligodendroglia and Microglia (Combined Method), Am. J. Path. **4**:153, 1928.

34. In our cases this method demonstrated acute swelling of the oligodendroglia. Normal forms of microglia were not always impregnated, although transitional stages were usually clearly shown. In the cases in which embalming was delayed for nine or ten hours, the microglia were poorly impregnated.

CHANGES IN MICROGLIA

Normal Aspects.—The microglia cells, under normal conditions, are most numerous in the gray matter; in fact, it is often difficult to demonstrate them in the white matter. They may be described as

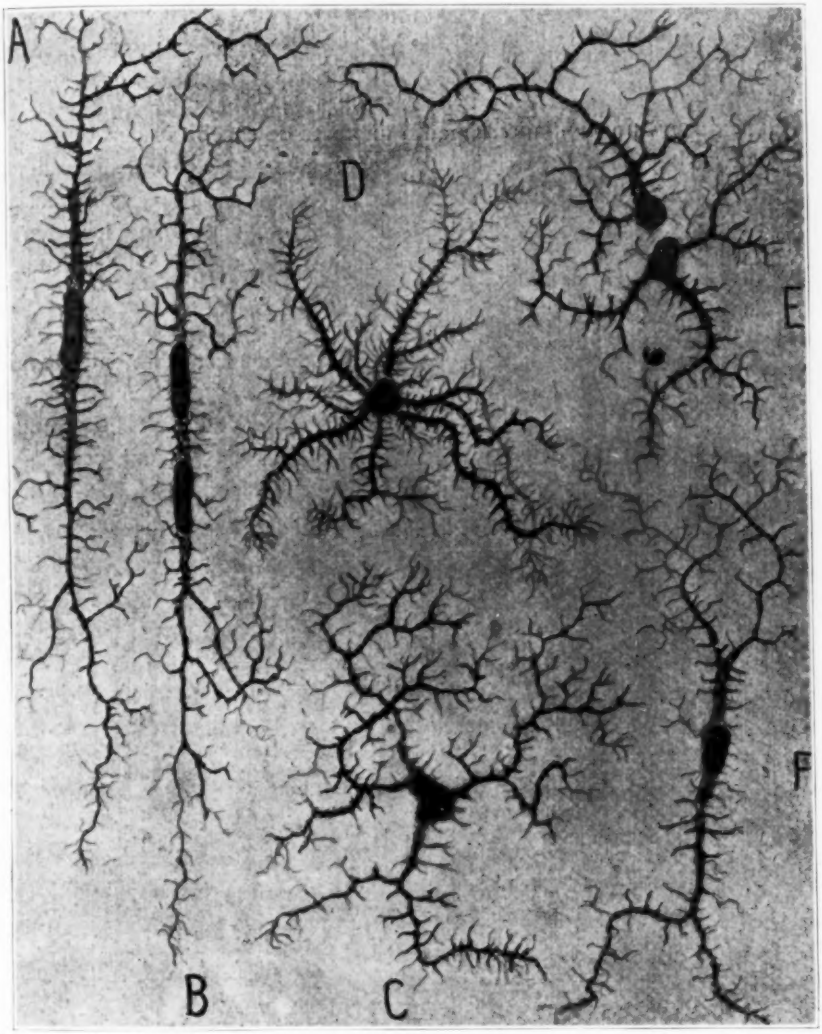

Fig. 1.—Normal forms of microglia. *A* shows a rod cell; *B*, a rod cell with two nuclei; *C* and *D*, multipolar cells; *E*, direct cell division, and *F*, a bipolar cell with bifurcated processes (after del Rio Hortega).

multipolar cells the processes of which present numerous simple or ramified side branches, resembling thorns on a briar (fig. 1). The cytoplasm is confined largely to the bases of the larger processes adjacent to the nucleus. It is very finely granular and, when clearly distinguished,

dustlike particles give it a ground glass appearance. No gliosomes, mitochrondria or centrosomes have been observed. It seems evident from the changes observed in these cells that the processes consist of a closely approximated cell membrane, with a minimum amount of interposed cytoplasm. These expansions are rather tortuous, and the terminal spines are set on them at irregular intervals. For example, some processes or parts of processes may be thickly studded with them, while others may have only a few for a considerable distance. The nucleus is round, roughly oval, triangular or, in some cases, depending on the shape of the cell, somewhat elongated. The nuclear membrane is well defined and usually presents no irregularities in its contour. The chromatin material tends to be collected into comparatively large granules varying in size and in number from two to ten or more. They are usually situated in the central portion of the nucleus; less often they are found lying against the nuclear membrane.

The number of processes varies, depending largely on the relationship of the cell to the surrounding structures. According to del Rio Hortega,[20] they may be classified as monopolar, bipolar and multipolar cells. The cell body consequently assumes a stellate, triangular or fusiform shape. The cells may be further classified from the standpoint of their morphologic relationship to other elements of the nervous system as follows: (1) perineuronal satellites, (2) perineuroglial satellites and (3) perivascular satellites. It seems best to add a fourth type, (4) the interfascicular cells, which, under certain conditions, probably have much to do with the formation of rod cells. The processes have a definite tendency to wrap themselves about these various elements, suggesting a protective function. Figure 1, taken from del Rio Hortega's original important contribution, illustrates some of the normal forms of microglia.

One point possibly of histologic importance has been observed in the study of microglia in this series. As already mentioned, these cells may occur as perineuronal, perineuroglial and perivascular satellites. The question arises as to whether these satellite cells are within or adjacent to the perineuronal, perineuroglial and perivascular spaces. In the instances in which the perineuronal space in particular was greatly distended with fluid, resulting from general cerebral edema, the microglial satellites were found to be pushed away from the nerve cell. This seems to indicate that these cells are normally outside the perineuronal as well as the perivascular spaces.

Response to Generalized Cerebral Changes.—Both local and general types of reaction occur in every case of serious injury of the head. The generalized changes may be essentially included under the heading of cerebral edema, together with frequent widespread petechial hemor-

rhages. Our observations seem to indicate that the microglia are practically unaffected by generalized edema. The only exceptions that we have found are an occasional vacuolization of the nucleus and a minor degree of swelling of the cytoplasm. It is possible that some of the vacuoles found in the cytoplasm and processes in transitional forms are of the nature of fluid. However, as near as can be determined by combining Penfield's and Herxheimer's methods, it seems that most of these vacuoles are unquestionably fat. In sections of undamaged brain tissue the microglia usually presented no changes that could be considered as outside the limits of normal. This was also true of cells situated just outside the area in which degenerative changes were taking place.

Reaction to Local Injury.—Local injury to the brain may be considered from the standpoint of contusion and laceration, of hemorrhage and of infection, the latter in the form of abscess or meningitis. There was no case of abscess of the brain in the present series, but it is doubtful whether the microglia would show any different change in an abscess secondary to injury than in one produced by any other cause. We have studied the changes in microglia in cases of abscess of the brain of otitic and metastatic origin and have found the typical transitional changes leading to the formation of compound granular corpuscles. It seems unnecessary to consider this complication further in this connection. We will have occasion later to mention the changes of subpial microglia in meningitis.

Contusion and Laceration of the Brain: These conditions are common accompaniments of injury to the head. We have been fortunate in securing material that demonstrated contusions and lacerations of various degrees and durations. The series includes cases of contusions of the brain in persons who were killed outright, as well as in those who survived for varying intervals up to a month or more. We have found that changes in the microglia depend directly on the severity of the contusion, its age and the proximity of the individual cell to the point of greatest injury. The degree and time of the appearance of change in the microglia depend on the severity of the injury. In a person killed outright (case 19), who suffered a moderate contusion of the right temporal lobe, the regional microglia were unchanged. A second instance (case 15), in which the patient may have lived half an hour, showed the microglia to be unchanged, although no gross local contusion was found. In another person (case 1), who lived for three quarters of an hour, the microglia in the region of a laceration in the right temporal lobe showed early changes characterized by vacuolization and coarse granulation of the cytoplasm. Of four patients who survived between one and two hours (cases 3, 13, 14 and 17), the microglia adjacent to

contusions and lacerations were unchanged in three, and showed early changes in one (case 13). The only case showing change was that of a boy aged 10. This suggests that age may have some bearing on the activity of these cells, particularly in view of the fact that the contusions were more severe in the older patients than in the boy. There are probably other factors entering into the process which we do not now fully appreciate. In a man surviving an injury about six hours (case 5), active amitotic division of the microglia with early swelling of the processes was already conspicuous in the region of a contusion of the right temporal lobe. Similar changes were found in a contused area of the left temporal lobe in another person of about the same age living twelve hours (case 23). In case 10, that of a patient who lived fourteen hours, only minor changes were found in the microglia, but again no localized gross contusions of the brain were found. In case 11, in which the patient survived about twenty-four hours, there was an extensive laceration of the left temporal lobe. Marked transitional changes and direct cell division of the microglia were found in the contused area. There was extensive swelling of the cytoplasm of all the major processes that contained coarse granules and variously sized vacuoles. In an older patient (case 24), surviving about the same length of time but having no bruising of the cortex, only the earliest changes in the microglia were present. In a patient, aged 17, who lived for fifty-six hours after an injury (case 21), with moderate contusions of the left temporal lobe, amitotic cell division and early changes in the microglia were found. One would expect greater changes in this case, considering the relatively long period of survival and the character of the gross changes. However, a period of ten hours elapsed between death and tissue fixation, allowing ample time for postmortem changes, which conceivably may have altered the histopathologic picture. In another person living almost four days (case 6), with multiple contusions of the left frontal and temporal lobes, transitional forms up to the formation of compound granular corpuscles were found. Both mitotic and amitotic cell division were actively taking place. In case 9, that of a man with a survival period of two weeks, having a diffuse contusion of the left frontal lobe, transitional forms and compound granular corpuscles were observed. Many of the cells contained two or more nuclei. In one patient living thirty-eight days (case 7) after extensive laceration of the left temporal lobe, the damaged area was found filled with fully developed compound granular corpuscles.

The reaction of the microglia to hemorrhage seems to be a somewhat different story. From our observations in cases presenting extensive subarachnoid hemorrhage, it seems evident that the unaltered blood fails to stimulate any change in microglia. It further appears that intracortical hemorrhage unaccompanied by any degree of bruising fails to

produce alterations in the microglia until the red blood cells undergo regressive change. This is also true of multiple petechial hemorrhages found in the white matter of the brain. In our series there were four cases that presented gross intracerebral hemorrhage. In a patient surviving a large hemorrhage in the left temporal lobe for thirty-one hours (case 2), only minor transitional changes were found. In the microglia at the margin of the hemorrhagic area active amitotic cell division was taking place. In another patient (case 20) surviving a massive hemorrhage in the left temporal lobe for five days, all transitional stages up to the formation of compound granular corpuscles were found. Extensive phagocytosis (case 4) by compound granular corpuscles was taking place in the wall of such an area after seven months.

Petechial hemorrhages in a bruised cortex or those within the white substance fail to stimulate any change in the microglia for several days. As previously suggested, this is probably due to the fact that the red blood cells do not break down during this period. In a patient who suffered a fracture of the left femur and both bones of the left forearm and survived for four and one-half days (case 8), multiple widespread petechial hemorrhages were found in the white matter. Herxheimer's method revealed fat emboli in the blood vessels in many of these hemorrhagic foci. With the combined method, compound granular corpuscles were found in the embolic areas. In another patient in whom were found multiple petechial hemorrhages and who survived an injury for six and one-half days (case 22), the brain presented similar changes with the formation of compound granular corpuscles. After breaking up of the red blood cells, together with regressive changes in the involved area, evidently occurring about the third day, there is a prompt formation of phagocytic cells. While it is true that compound granular corpuscles are not produced until there is some degenerative change in the red blood cells or in the tissue in the involved area, these phagocytes ingest the few remaining unaltered red blood cells as well as hematogenous débris. Macklin and Macklin [35] observed inclusions of red blood cells in macrophages in experimental brain wounds in rats, and Wilson [36] observed similar conditions in the human being following a cerebral puncture wound. As no normal microglia cells were found in the vicinity of these embolic areas, we assume that the phagocytes have their origin, at least to some extent, in the connective tissue of the blood vessel wall.

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35. Macklin, C. C., and Macklin, M. T.: A Study of Brain Repair in the Rat by the Use of Trypan Blue, with Special Reference to Vital Staining of the Macrophages, Arch. Neurol. & Psychiat. **3**:353 (April) 1920.

36. Wilson, Richard B.: Brain Repair, Arch. Neurol. & Psychiat. **15**:75 (Jan.) 1926.

Practically all investigators of changes in the brain following experimental injury have found that transitional stages up to the formation of compound granular corpuscles may be present by the end of the first day. Del Rio Hortega [25] found advanced transitional changes at the end of twelve hours and compound granular corpuscles at the end of twenty-four hours. Farrar [29] found macrophages filled with fat as early as after eighteen hours in experimental injuries. These phagocytic cells were present as long as degenerated tissue remained in the region of the wound. In our human material we have found early changes consisting of swelling of the major processes and cytoplasm within two hours after injury. Transitional forms that might be recognized as well defined stages in the development of compound granular corpuscles were first seen after twenty-four hours. In contused brains no fully developed compound granular corpuscles were found until almost four days after injury. This also appeared to be the case in gross intracranial hemorrhage, in which transitional stages were found at the end of two days and compound granular corpuscles at the end of five days. Fully developed phagocytes were found in the vicinity of petechial hemorrhage at the end of four and a half days. From these observations we believe that there is either a fundamental difference in time reaction of microglia cells in animals and those of man, or that conditions under which the observations were made were essentially different. As far as we have been able to determine, no one has had occasion to study the microglial changes about a puncture wound in a human brain earlier than from six (Wilson [36]) to ten (Cone [24]) days after the injury. It is readily recognized that in most cases of contusion the injury is more or less diffuse, and only in cases of a clear-cut laceration would circumstances be at all parallel. To the present moment we cannot draw final conclusions as to the comparison between clean puncture wounds in experimental animals and diffuse contusions following injury to the human brain.

The Course of Microglial Change.—In this section we shall attempt to trace the changes in microglia from the earliest alteration of the normal up to the formation of compound granular corpuscles. This will include certain nuclear changes, as well as the mode of direct cell division. We shall also consider the various regressive changes that lead to complete destruction of the cell.

Transitional Stages: In studying the microglia in this series of cases of injury of the brain, several apparently well defined stages can be made out. They may be listed as follows: (1) early swelling of the major processes or a diffuse swelling of cytoplasm and all processes, (2) spider cell stage, (3) ameboid stage and (4) compound granular corpuscles.

The earliest transitional stage consists of a more or less diffuse swelling of the major processes, the cell body or both. In addition, there are a variable number of inclusion vacuoles. Considerable variation in the picture may be found, depending largely on the severity of

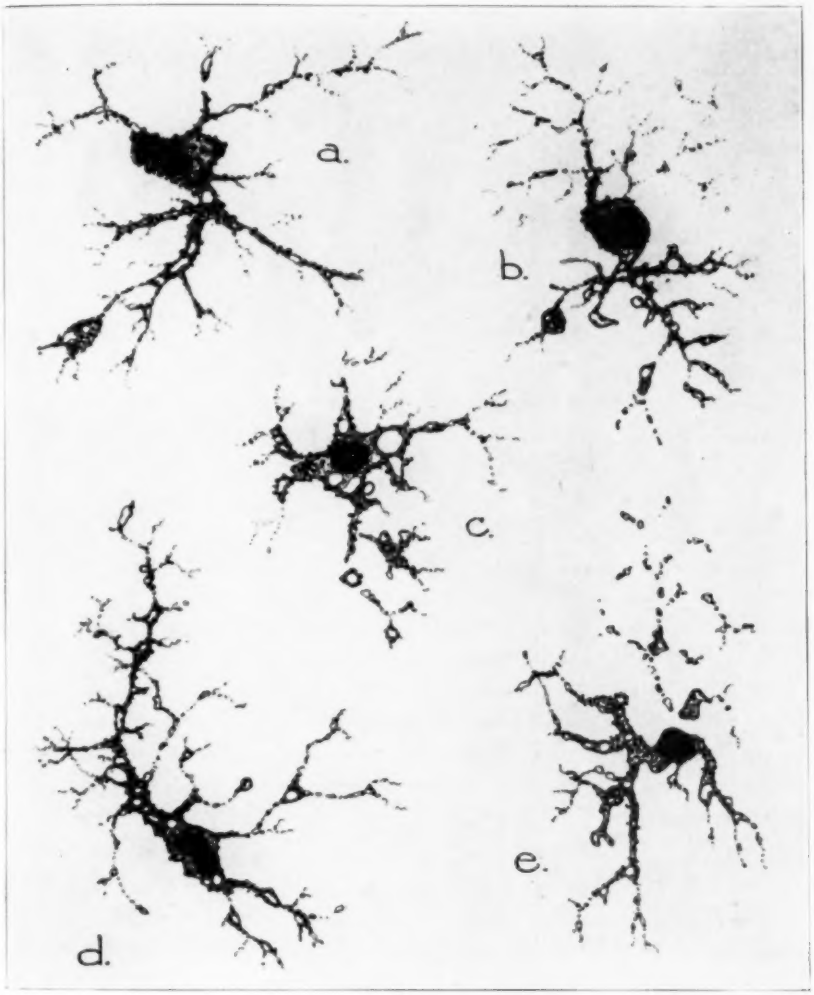

Fig. 2.—Early changes of microglia: *a.* and *b.*, binucleated cells showing mace-like swellings of processes; *c*, formation of large vacuoles in cell body with breaking off of expansions; *d*, small vacuoles in processes and branches; *e*, break ing up of major process.

the local injury. If it is marked, there is usually an early vacuolization of the cell processes with only a minor degree of swelling of the expansions or the cell body. In the cytoplasm, coarse granules usually make

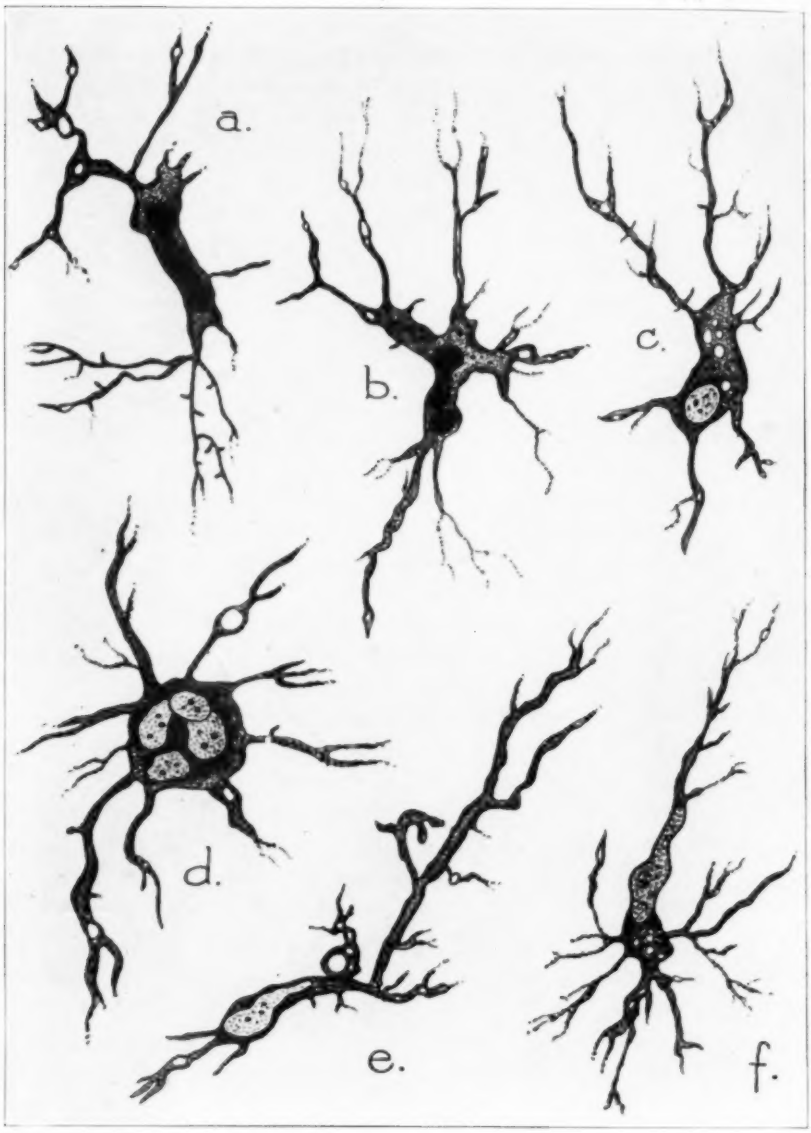

Fig. 3.—Early diffuse swelling of microglia. The loss of the terminal and lateral spines and the paucity of vacuoles are characteristic of this stage. The constriction of the nucleus, an early stage of direct cell division, is shown, *a;* the double nucleus, *b;* swelling of the cell body rather than of processes, *c;* multipolar multinucleated cell, *d;* swelling of major process, *e;* monopolar swelling of cytoplasm, *f*. This stage is contrasted with that shown in figure 2, in which there is an early appearance of coarse granulation and numerous vacuoles.

their appearance. They may be either an enlargement or a condensation of the normal granular elements, or possibly represent phagocytosis of unchanged débris. Their early appearance and their globoid shape favor the first conception. The appearance of cells of this type is indicated in figure 2. The patient was a man, aged 28, who survived an injury only six and three-fourth hours, which suggests that the change probably represents a rapid process following a severe local injury.

The opposite extreme of this stage is represented by a major degree of swelling of the cytoplasm with only the occasional appearance of vacuoles. The change probably is indicative of a slower process, for these cells were found in the brain in case 9, that of a patient who survived a minor bruising of the cortex for fourteen days. The cytoplasm resembled that of the normal cell, except that it was increased in amount. This swelling of the cell body was accompanied by a disappearance of many of the terminal and lateral spines. Moderate-sized vacuoles were present in small numbers, either in the cytoplasm of the cell body or in the major processes (fig. 3). Between the former and the latter type of cell change all variations undoubtedly occur, depending on the speed with which the reaction takes place.

Swelling does not necessarily involve all of the cytoplasm of the cell body and processes symmetrically. It is not uncommon to find one or more major processes swollen while the cell body remains comparatively unchanged, or vice versa. In a severely injured area, cells may be seen in which one portion is undergoing a regressive change while another is actively phagocytosing débris. Major processes in such a case may be represented only by a branchlike arrangement of coarse granules. Macelike swellings indicate that even one portion of an expansion may be more active than another. These phenomena appear to be more common in lacerations attended with greater tissue destruction than in simple contusion.

The vacuoles represent phagocytosed brain tissue that has been broken down from its complex lipoid structure into free fat. If this chemical process takes place rapidly, as appears to be the case in lacerated regions, one finds an early appearance of minute vacuoles in the smaller radicals of the cell expansions. One or more larger vacuoles may be seen in the major expansions or cell body, and may be so large that rupture through the cell membrane occurs. The fatty nature of these "vacuoles" is demonstrated when the silver preparation is counterstained with scarlet red. The likelihood that some of them may be of a watery nature seems very remote, as indicated by the absence of such vacuoles in the cell body in other portions of an edematous brain. Vacuoles sometimes seen in the nuclei may be of a fluid nature.

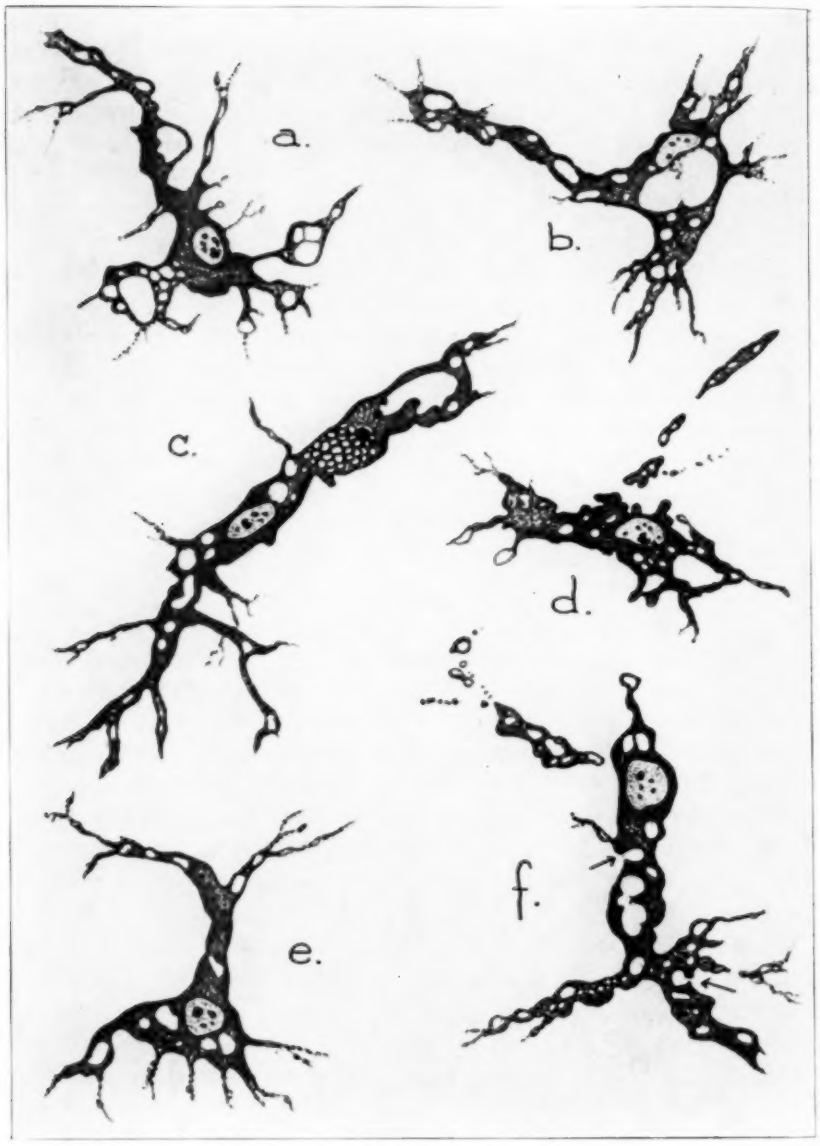

Fig. 4.—Spider cell stage of transitional microglia. These stages are: *a* and *b*, marked swelling of the major processes; *c*, swelling of cytoplasm, with small vacuoles giving a lacelike appearance to one circumscribed area, and *d*, breaking off of a large process. This is shown also in *f*. In *e*, swelling of a perineural satellite is shown; in *f*, arrows point to vacuoles that have ruptured through the cell membrane.

Nuclear changes make their appearance in this early stage. Condensation and agglutination of the chromatin granules soon transform the more or less vesicular nucleus into a round or oval, solid black mass. This is particularly true if the section has been even slightly overimpregnated. All stages of direct cell division soon take place, and multinucleated cells may be found a comparatively short time after injury.

The spider cell stage is characterized by a diffuse swelling of all the larger processes, with a loss of the smaller radicals (fig. 4). These cells are markedly distended, with variously sized vacuoles, many of which are large. Usually a smaller number of coarse granules are present. Rupture of large adjacent vacuoles frequently gives rise to ragged cystlike spaces within the cell. There are often multiple points of rupture of the vacuoles, through the cell wall, which are frequently responsible for separation of the larger processes from the cell body. Some of the processes are still small, marked only by the presence of small vacuoles that separate the usually approximated cell wall on either side. Small vacuoles are often lodged at the points of bifurcation of the processes. Rows or groups of cells undergoing such change may be found entwined about blood vessels or nerve cells. Fragmentation of the processes with granular degeneration may be found near the point of greatest damage. The nuclei of the cells situated near a laceration are often very large, and may represent the early stage of direct cell division.

The ameboid stage is the forerunner of the typical compound granular corpuscles (fig. 5). It is characterized by a markedly irregular contour of the cell body, the presence of numerous large vacuoles and only an occasional long process. There is a wide variety in the form and shape of these cells. This irregularity is due to the protrusion of certain portions of the cell in all directions or the persistence of the stumps of the larger processes. Small separated spheroidal masses adjacent to the cell suggest that they may be parts of broken-off processes. In certain portions of the cell coarse granulations may be found, usually perinuclear or peripheral in situation. These granules may appear as chains between the vacuoles. The vacuoles are usually large and give the cytoplasm a foamy appearance. Only occasionally are irregular vacuoles or rupture through the cell membrane to be found. The asymmetry of cellular reaction is suggested by the occurrence of one or more fairly normal processes still attached to one pole of the cell.

Of especial interest are the peculiar nuclear forms in these cells observed especially in the brain in case 4. The chromatin content of the nuclei often presented a rather irregular distribution. In some it occurred in the form of a large irregular, centrally situated mass. In

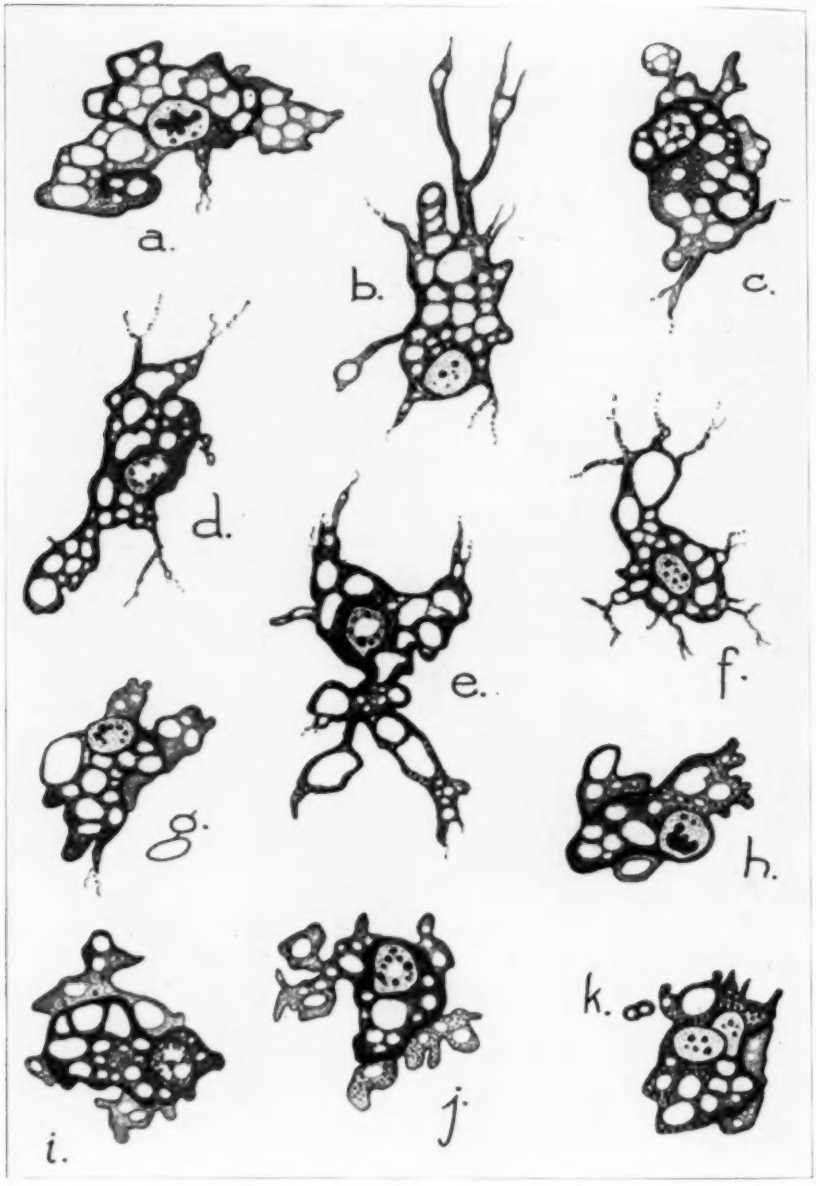

Fig. 5.—Ameboid stage of transitional microglia. Peculiar nuclear appearances are often seen. In *c*, *d*, *e*, *i* and *j* vacuolated nuclei are shown; in *a* and *h*, the agglutination of nuclear chromatin; *b*, *d*, *e* and *f* still retain expansions. In *k*, a binucleated form is shown.

others, two or three smaller irregular masses were found. In still others, it appeared as crescents or rings. At times it was scattered rather evenly throughout the nucleus. One or more vacuoles within the nucleus gave rise to peculiar chromatin patterns, such as ring or wheel arrangements. The latter resembled closely the nuclei of plasma cells. Cell division seems to occur almost entirely by amitosis, two or more nuclei often being found within a single cell. The nuclei in the ameboid forms tend to assume a peripheral situation, owing to an accumulation of vacuoles within their cytoplasm.

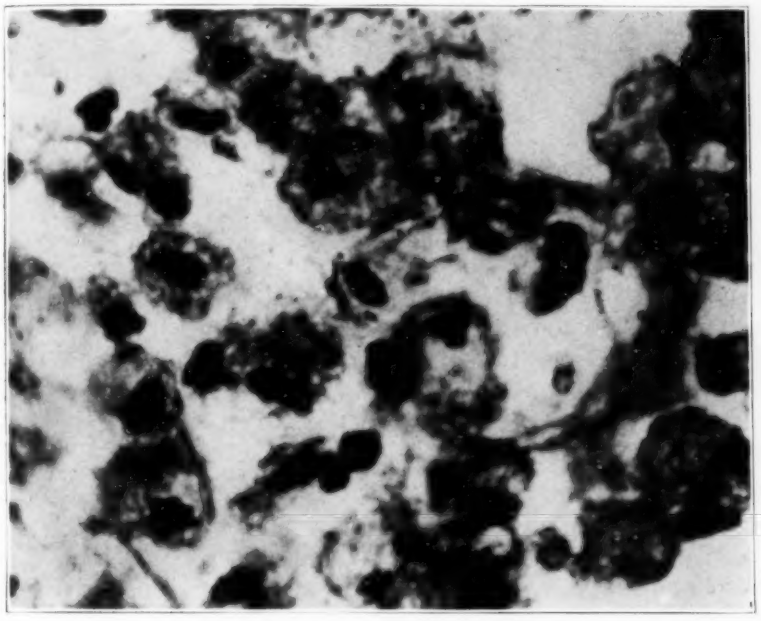

Fig. 6.—Compound granular corpuscles in degenerating brain adjacent to an old laceration in case 7 (death in thirty-eight days). Penfield's combined method; × 700.

The appearance of compound granular corpuscles is so well known that a detailed description is scarcely warranted. A few special observations may be mentioned. These cells are characterized by their round, apolar contour, their fairly uniform size and by the presence of vacuoles of various sizes which fill the cytoplasm (fig. 6). Coarse black granules of variable number may be present in addition to the vacuoles. If the vacuoles are small, the cytoplasm has a lacelike appearance. Rupture of vacuoles through the cell membrane is still occasionally seen. The nuclei, as a rule, are small and dark, and only rarely is more than one nucleus found in a cell. Pyknosis of the nucleus, indicated by a shrink-

ing from the surrounding cytoplasm, sometimes gives rise to a perinuclear halo. In cases having a longer survival period, case 4 for example, peculiar nuclear changes, as described under the previous stage, may also be found. The final transition leading to the formation of fully developed phagocytes may consist of the loss of a single, often comparatively unchanged, process.

Fully developed macrophages are found in more or less extensively damaged brain tissue, appearing about the fourth day after injury. As previously mentioned, their development is stimulated by regressive stages taking place in the various individual elements. They are usually seen in numbers only in areas in which the normal structures have been reduced to débris. In cases of contusion or laceration, macrophages were found in a narrow zone along the margins of the laceration or associated hemorrhage. A rather interesting arrangement of these cells was observed in case 7. The patient survived a rather extensive laceration of the posterior part of the left temporal lobe for thirty-eight days. Bordering the laceration, several well defined layers could be distinguished. In a narrow zone along the laceration a few phagocytes were found loaded with yellowish-brown pigment, evidently of hematogenous origin. A second wider zone of scar tissue formation contained numerous phagocytes and some fibrous astrocytes. A third comparatively acellular zone, of varying width, revealed scattered patches of gliosis with comparatively few macrophages. In a fourth zone extending into the surrounding cortex, there was a reactive gliosis with hypertrophy and proliferation of the astrocytes. Early transitional forms of microglia and moderate acute swelling of the oligodendroglia were also present.

The distribution of compound granular corpuscles in the margin of secondary cerebral hemorrhage is worthy of mention. In case 20, with a survival period of about five days, a narrow marginal zone was marked with pigment-laden cells. A wider strip of softened cerebral tissue was marked by various transitional stages up to fully developed compound granular corpuscles. Of particular interest were the more or less circumscribed groups of phagocytes occupying the sites of secondary hemorrhage (fig. 7). Following the same process in case 4, that of a patient who survived an intracerebral hemorrhage for over seven months, we found a very narrow superficial zone of connective tissue and regional gliosis. Beneath this, there was a comparatively acellular zone marked by patches of gliosis. Macrophages were found in comparatively small numbers in this region and more abundantly in localized patches that were evidently the sites of smaller secondary hemorrhages. The latter were by no means so pronounced and circumscribed as in case 20. Such areas were most conspicuous about

irregular zones of broken-up tissue in which there were only feeble attempts at fibrosis or gliosis.

As a result of our observations, we are not in accord with the belief that rod cells are a stage in the formation of compound granular corpuscles. To the contrary, they are the slightly altered fusiform or bipolar, interfascicular elements. We were struck with their relative infrequency in all the cases studied. They were found more commonly in case 6, that of a patient who survived an injury for almost four days. When present, they consisted merely of early changes in the fusiform

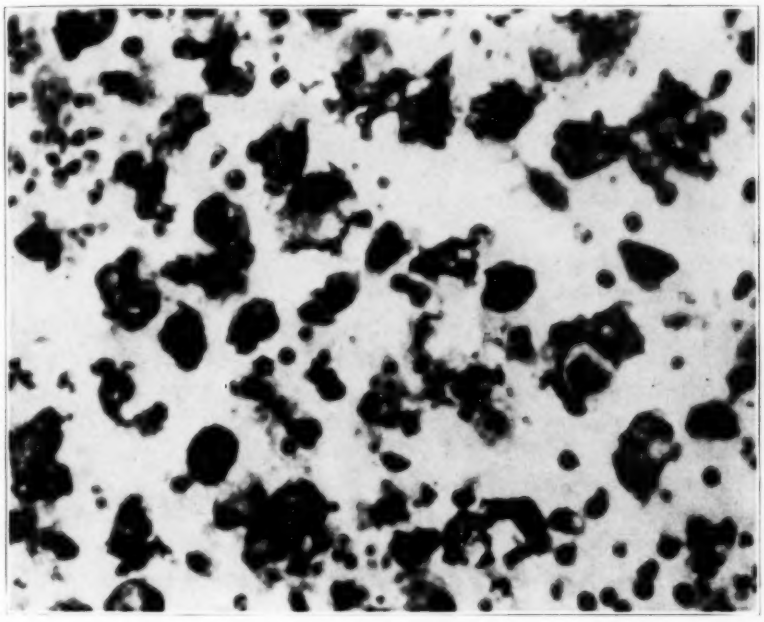

Fig. 7.—Ameboid forms and compound granular corpuscles in a hemorrhagic area in case 20 (death in five days). These cells were actively phagocytosing unchanged, as well as broken down, red blood cells. Penfield's combined method; × 320.

cells. None of the typical rod cells of Nissl were observed, except in one patient (case 12) who undoubtedly had dementia paralytica. The injury to the head, of a minor degree, was sustained by a fall during a seizure. The combined method demonstrated the typical rod-shaped microglia. It is our opinion that rod cells as such occur in chronic or subacute conditions in which the cortical nerve fibers, as well as the cells, are undergoing a change of lesser degree.

While the various stages have been described separately, in many instances all transitional forms up to compound granular corpuscles

have been found in a single case. The latest stage reached in the process as determined by histologic examination appears to depend on the period of survival and the severity and nature of the injury. Beginning with fairly normal forms in the somewhat remote cortex, and approaching the injured area, all stages may be traced in a single case.

As previously stated, we are not entering into a detailed discussion of changes following infectious processes, because, in the first place, they are complications and not the direct results of injury to the head. In the second place, the observations are already well known. It might not be out of order to state a single observation in a case of meningitis (case 18) following an injury to the head. The subpial microglia showed an early and minor swelling of the major processes, while the deeper cells remained unchanged.

Regressive Changes: Under certain conditions microglia cells, like other cellular elements, undergo degenerative changes from which they do not recover. Penfield [31] has described alterations in the various cell types as a reversible process; that is, under certain conditions a cell may perform its normal functions while at the same time it is undergoing certain alterations in its structure. If the cell has been badly damaged, it may not recover but may go on to complete destruction. On the other hand, if not too severely damaged the cell may return to a normal state. It has been of interest to follow the various methods by which degeneration takes place. These degenerative forms are found entirely in a narrow zone adjacent to lacerations or along the margins of hemorrhagic cavities. It is likely that these cells share the common fate of the other elements in this zone. Degenerative forms assume a variety of appearances (fig. 8). They may be present as somewhat shrunken, transitional forms the nuclei of which are pyknotic. The shape and situation of the degenerated cell may be indicated by an irregular mass of coarse granules unenclosed by a membrane. The nucleus is indicated by a single large granule or by a clump of smaller granules. At times an irregular form, characterized by large granules and an irregular pyknotic nucleus embedded in a finely granular cytoplasmic mass, may be observed. A rather common type of change is one that we have come to call an "explosion form." In this type there is a bursting of the cell membrane with a scattering of the finely granular cytoplasm intermingled with coarser granules, appearing not unlike the explosion of a charge set in the ground. It seems evident that these regressive changes do not necessarily involve the entire cell simultaneously. It is not unusual to see one portion of the cell apparently viable, while the processes arising from another situation are indicated only by an irregular mass of granular débris. Furthermore, one may see a cell body undergoing regressive change while one or more macelike processes still appear viable. Finally, some of them are indicated only

by a shadow or ghost form, characterized by a more or less finely granular outline of the original cell. It is evident that destruction may overtake the cell in any of its developmental stages, for we have frequently observed the breaking up of fully formed macrophages as well as transitional forms.

Cell Division in the Microglia.—While not bearing so directly on the problem of cell change in injuries, we have been interested in following the method of cell division, as it indicates to some degree the biologic characteristics of this element. It has been shown already that amitotic cell division of the microglia may begin within a few hours after injury.

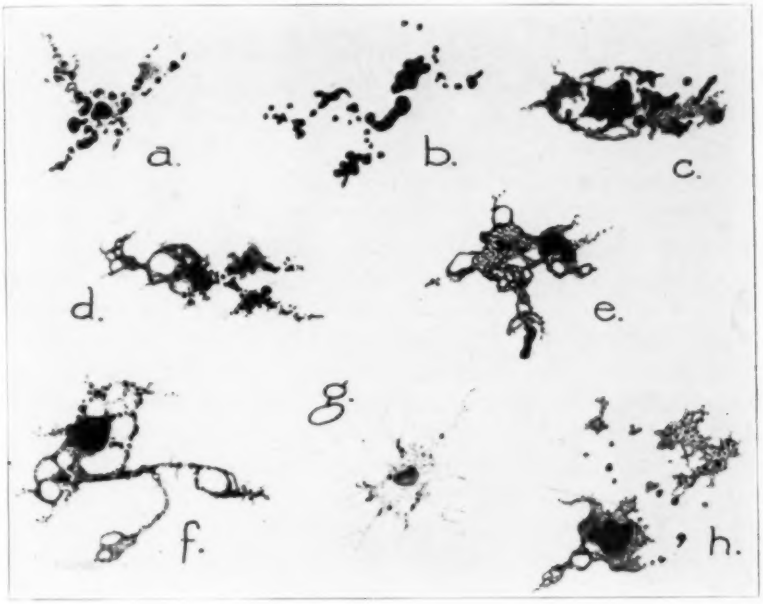

Fig. 8.—Regressive changes in microglia: *a*, *b* and *c*, various stages in breaking up of cells; *d*, granular destruction of one portion of cell, while opposite pole remains viable; *e*, shrinking of cell with pyknosis; *f*, granular degeneration of the cell membrane and cytoplasm at one pole, the balance of the cytoplasm and processes appearing viable; *g*, "ghost form"; *h*, "explosion form."

Cells with two or more nuclei may be found in any of the various transitional stages. The process of cell division can be traced most easily when it is fairly active in the presence of a moderate injury to the brain. In direct cell division, early stages appear as an enlargement of the nucleus followed by indentation and constriction of its membrane. Indentations indicating the future formation of three nuclei from a single elongated nucleus have been observed. Following this there is a complete separation into two or more nuclei by an intervening wall.

The influence of certain factors on the mode of cell division has been interesting to follow (fig. 9). It seems fairly certain that the position of the larger processes influences the direction of the line of cell cleavage. A fusiform or bipolar cell will usually divide through the midportion of the nucleus in a transverse direction, as has been illustrated by del Rio Hortega (fig. 1). In a cell with three major processes the nucleus will often divide longitudinally, the first evidence of division appearing adjacent to the interval between the two more closely approximated processes. If a large process comes off at right angles, the nucleus may become "T" shaped before division takes place. In multipolar cells,

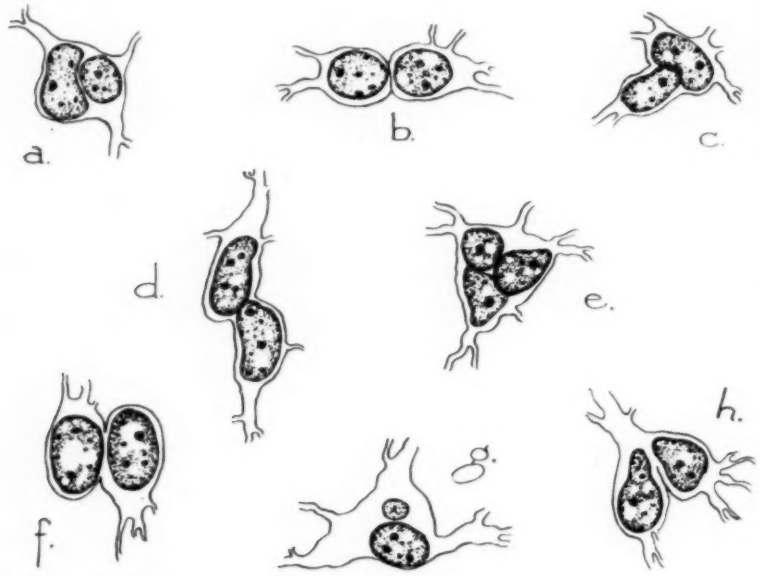

Fig. 9.—Modes of direct cell division in microglia: *a*, division into two unequal nuclei; *b* and *d*, types of nuclear division in rod cell; *c*, nuclear division resulting from lateral budding; *e*, multinuclear division in multipolar cell; *f*, nuclear division in lateral plane; *g*, "polar body" type of nuclear division; *h*, type of nuclear division following splitting of the cell between two major processes.

division is often irregular, with three or even more nuclei being found within the confines of a single cell membrane.

Nuclear division is not necessarily uniform; that is, division is not made into two or more nuclei of equal size. On occasion, one sees one large well developed nucleus with a smaller one adjacent to it, appearing like a "polar body." We have never observed more than one such "polar body" in a single cell. Its significance is not clear. Del Rio Hortega and Penfield [27] found mitotic figures in compound granular corpuscles as early as the third day, but did not state the method of cell division in the

transitional forms. Del Rio Hortega [20] did not show any mitotic figures in his excellent illustrations of transitional forms of microglia, but binuclear and dividing forms seem to indicate that direct cell division is taking place. We have found mitotic figures only in cells in situations where compound granular corpuscles were abundant. Here were occasionally observed mitotic figures in large cells in close proximity to blood vessels. While it could not be determined with certainty, it was suggested by their position and association that they were completely transformed microglia. The comparative infrequency of binucleated compound granular corpuscles may be taken as indirect evidence pointing to the same conclusion. In other words, in the fully developed macrophage cell division may be either direct or indirect, while in the transitional forms direct cell division seems to be the rule.

Considerations of Microglia Function.—It is generally recognized that the function of microglia is primarily the phagocytosis of broken-down cellular and fibrous elements of the brain. In the absence of demonstrable destructive change, only minor alterations in this element are found. Early swelling of the primary processes may be seen in the subpial cortex in meningitis, or as a more or less diffuse response in injuries to the brain. Any stage beyond this early alteration is found only when tissue is undergoing degeneration. It is likely that the stimulation is essentially a chemical one resulting from a breaking down of cell protoplasm. In cases of hemorrhage, the reaction seems to be postponed until an actual destruction of the red blood cells occurs. In this connection it is interesting to note that, when once developed, the phagocytes are capable of ingesting morphologically intact as well as altered red blood cells.

Another clue as to the possible function of microglia lies in their morphologic relationship to the other elements. Their processes may be found entwined about nerve cells, astrocytes and blood vessels, and the interfascicular cells (fusiform or bipolar cells) are situated between the nerve fibers that enter the cortex. When the cortex is injured, the microglia about the nerve cells in the damaged area seem to undergo a more marked degree of change than those situated about other elements. This would suggest that the microglia in these situations have a protective as well as phagocytic function. It is also a common observation to find fairly well advanced transitional forms about the blood vessels, often forming long chains. We do not know the significance of this phenomenon. Finally, the interfascicular glia probably have a protective function for the intracortical nerve terminations. In this sense they may be counterparts of the interfascicular oligodendroglia.

The phagocytosed products are chiefly free fat derived from broken-down cell and nerve sheath lipoids. Some of the coarse dark granules are probably derived from degenerating astrocytes. We have not

observed clasmatodendrosis to the same extent that Cajal [17] and Penfield [23] have so well illustrated. It was present to some extent in case 7 in the area of regional gliosis adjacent to an old laceration in the brain. Here one observed phagocytes attached to the expansions of some of the degenerating astrocytes. The process will be described further in a later contribution. We have had occasion to see phagocytosed myelin from nerve fibers undergoing regressive change at the margin of invasive gliomas. If actual destruction of nerve fibers took place in the later stages of injury to the brain, similar phenomena would probably be observed. In conclusion, we would say that the microglia have a primary phagocytic function, and probably a secondary limited protective reaction.

CHANGES IN OLIGODENDROGLIA

Normal Aspects.—The oligodendroglia make their appearance in later embryonic life, and proliferate rapidly at about the time of birth. The cell cytoplasm is abundant, and the gliosomes are large. Del Rio Hortega [19] believed that gliosomes play an active part in the formation of myelin. The successive stages in the development of this cell have not been fully traced. Some believe that they arise from gliablasts, but this theory is open to question.

Later in life, the cytoplasm becomes granular and small. The cell body assumes a rounded or oval shape, and the processes arise from small angular expansions of the cytoplasm. The processes are slender and may be studded with fine granules. Their ramifications are extremely simple, and division beyond secondary or tertiary branches is most unusual. These ramifications are probably greater in the human being than in lower animals, and show a larger number of swellings at the points of division. These swellings appear as oval vacuoles, but it is likely that they are granules unimpregnated by the silver stain.

The oligodendroglia, like the microglia, have been classified from the standpoint of their position. The interfascicular glia are found in rows between myelinated nerve fibers in the white substance. The processes are intimately associated with the myelin sheath, the longer ones lying in the long axis of the nerve fiber. The shorter processes pass around the myelin sheath. A second group, the perineuronal satellites, are found in the hollows between the neuronal processes. Microglia are sometimes found in the position of a perineuronal satellite, but the larger proportion of them are oligodendroglia. It has been established that the oligodendroglia are most numerous in the white matter, while the microglia are most abundant in the cortical gray substance. From this, it may be surmised that each type of cell has its own particular function, with perhaps some overlapping under certain conditions.

Response to General Injury.—In this study it has become apparent that the response of the oligodendroglia to injury is usually general rather than local. On the contrary, in early or in very late cases we have seen instances in which it has seemed to us that the reaction has been more local than general. For example, in patients surviving an injury for only a few hours, the oligodendroglia showed more reaction adjacent to a cortical injury than at some distance from it. Furthermore, in a patient living for seven months following an injury to the head, the oligodendroglia in the white matter showed no detectable change, while those in the adjacent cerebral cortex still showed evidence of swelling. We have concluded from this that there may be a localized

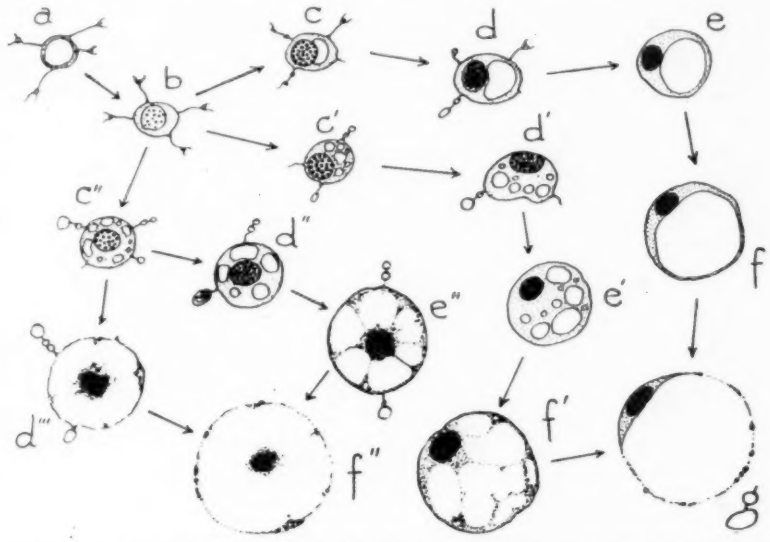

Fig. 10.—Acute swelling of the oligodendroglia. Schematic illustration leading to typical forms of acute swelling: *a*, normal oligodendroglia; *b*, granular swelling of cytoplasm; *c* to *g*, formation of a single large vacuole resulting in "signet ring" forms; *c'* to *f'*, eccentric vacuolization leading to ultimate "signet ring" forms; *c"* to *f"*, stages of typical wheel forms leading to extensively swollen cell with centrally placed nucleus; *d'"* indicates a transitional stage when the process is more rapid than in *d"*.

reaction appearing first about the injured area, which later becomes generalized. Even after the general reaction has subsided, this localized reaction persists as long as there is evidence of focal injury.

General Response of Oligodendroglia.—Acute swelling of the oligodendroglia was found to be characteristically present in all cases. More or less uniformly it occurred in all portions of the brain. This was in accord with the observation of Ferraro and Davidoff [32] in experimental injuries. Penfield and Cone [31] failed to find changes in the

oligodendroglia in pieces of brain tissue coming from the ear of a person who had suffered a basal fracture of the skull. While not having specific metallic methods at their command, the illustrations of Farrar [29] and Cajal [37] indicate that such cells were seen in the brain following experimental injury. They clearly show the signet ring and wheel forms that are now recognized in acute swelling of oligodendroglia.

The time of onset and course of development of acute swelling in these cells have been traced with considerable interest (fig. 10). That it is a prompt and active response is shown in case 19. This woman, aged 70, was practically killed outright, and tissue fixation was begun within half an hour. The oligodendroglia revealed early changes that consisted of small discrete vacuoles in the cytoplasm. In case 15, in which a man, aged 48, died within thirty minutes after an injury, there was a marked widespread acute swelling of the oligodendroglia, some of the cells already having ruptured. In the brain of a woman, aged 63, who survived an injury for only three quarters of an hour (case 1), there were extensive acute swelling and even rupture of some of the cells. In case 17, that of a patient surviving for one and a quarter hours, acute swelling of the oligodendroglia was present, and constriction of some of the nuclei indicated an early attempt at direct cell division. In case 3, that of a patient surviving for only two hours, binucleated forms were observed, which suggested that direct cell division had already taken place. That this process is not uniform or even constant is indicated by cases 13 and 14. In case 13, examination of the sections revealed that some of the oligodendroglia had undergone complete acute swelling, while others showed only early stages of the process, as characterized by a few small discrete vacuoles in the cytoplasm (fig. 11). Furthermore, sections of the brain in case 14, that of a woman who survived an injury for two hours, also showed a very minor degree of acute swelling. Age may well be a factor in the production of acute swelling, as in case 13, that of a boy, aged 10, the process was most advanced. In a man, aged 48 (case 3), the changes were less complete, and in case 14, that of a woman, aged 75, only a minor degree of vacuolization was present. This seemed significant, as all the patients had lived for about two hours following the injury. In case 11, that of a girl, aged 9, who lived for fifty-six hours, there was tremendous generalized swelling of the oligodendroglia with frequent rupture of the cell membrane. Other cases with a similar survival period consistently showed the same diffuse and marked swelling of the oligodendroglia.

In some cases, the beginning of the reversal process, by which these cells return to the normal state, apparently starts within a few days after

37. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928, vol. 2, p. 714.

the injury. In case 16, that of a patient who survived for three and a half days, there was very little evidence of acute swelling, most of the cells showing only a few small discrete vacuoles. This may be interpreted either as an early step toward normal restoration or as a lack of original acute swelling. Most of the cases of patients surviving from two days to a week showed typical acute swelling of marked degree, and in case 9, of a man, aged 32, who survived two weeks, these changes were still present. In case 7, that of a boy, aged 14, who died thirty-eight days after an injury, acute swelling was still present in the region of an

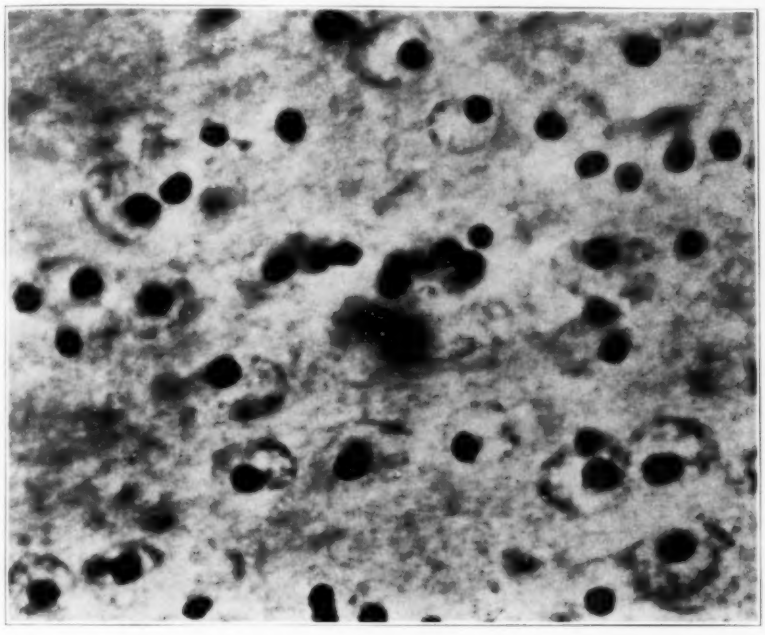

Fig. 11.—Acute swelling of oligodendroglia. Typical observations in acute injury to the head. Case 13 (death in two hours). Penfield's combined method; × 700.

extensive laceration. In this case, the oligodendroglia within the damaged area were undergoing destruction, while those more distant had a normal appearance.

It seems evident that acute swelling of the oligodendroglia is an early and almost consistent observation in the brains of persons suffering from extensive injury to the head. The process excited by trauma may continue after death, for it was present in a minor degree in a patient who was practically killed outright. It evidently progresses rapidly, for within a few hours the change may be fairly complete and widespread. It may be present as a general change for as long as two weeks, and has

been found near injured areas thirty-eight days after injury. A return to the normal state may begin within the first week, providing the injury was not too extensive, and continue until all evidence of local damage disappears. We have not been able to follow the details and time of restoration, as the very nature of the case precluded this possibility. One may assume that in cases of less severe injury with recovery, acute swelling of the oligodendroglia occurs and is followed by reversible changes leading to complete restoration of the cell.

Mode of Change in Oligodendroglia.—The transitional stages resulting in acute swelling of oligodendroglia depend on the speed with which the change takes place and the proximity of the cells to local injury. Such changes may be more easily traced when the process takes place more slowly. The cytoplasm of the cell becomes granular, sometimes coarsely so, resembling in this respect the coarse granulation of transitional forms of microglia. In such cells, small discrete vacuoles make their appearance. These vacuoles increase in size by gradual enlargement or by coalescing with other vacuoles. The granular cytoplasm becomes confined to a narrow rim at the periphery of the cell or condensed about the nucleus. The enlarging vacuoles progressively reduce the intervening cytoplasm to rows of variously sized granules, the "cytoplasmic girders" (Penfield and Cone [31]). Small masses of granules may be found adjacent to the nucleus or the cell wall.

In the meantime, the processes gradually drop off or undergo certain changes which are of considerable interest. The processes may be occupied by numerous round, oval or elongated vacuoles. They are not all involved symmetrically. In many instances, one or more processes appear normal, while the others may be lost or undergo change. One rather interesting type of alteration is that of the macelike swelling. These are characterized by small round or oval enlargements containing coarse granules and vacuoles. They first appear at the point of division of the process into its two terminal filaments. As it gradually enlarges, the terminal processes are lost, and the swelling stands out at the end of the expansion. At times several swellings may occur in a single expansion, giving the appearance of a short string of beads. The processes gradually drop off until the cell becomes rounded. Many of these rounded cells retain a single and often fairly normal process, or an attached globular swelling indicating where such a process had existed. The change in the shape of the cells during the transformation is also of interest. Originally round, oval or slightly irregular in the early stages, they assume many peculiar and irregular contours. This is due to an asymmetric vacuolization of the cytoplasm and to alterations in the expansions. At times these cells are so irregular as to make it somewhat difficult to distinguish between them and transitional forms of microglia. With the increase in size and number of the vacuoles and loss of expan-

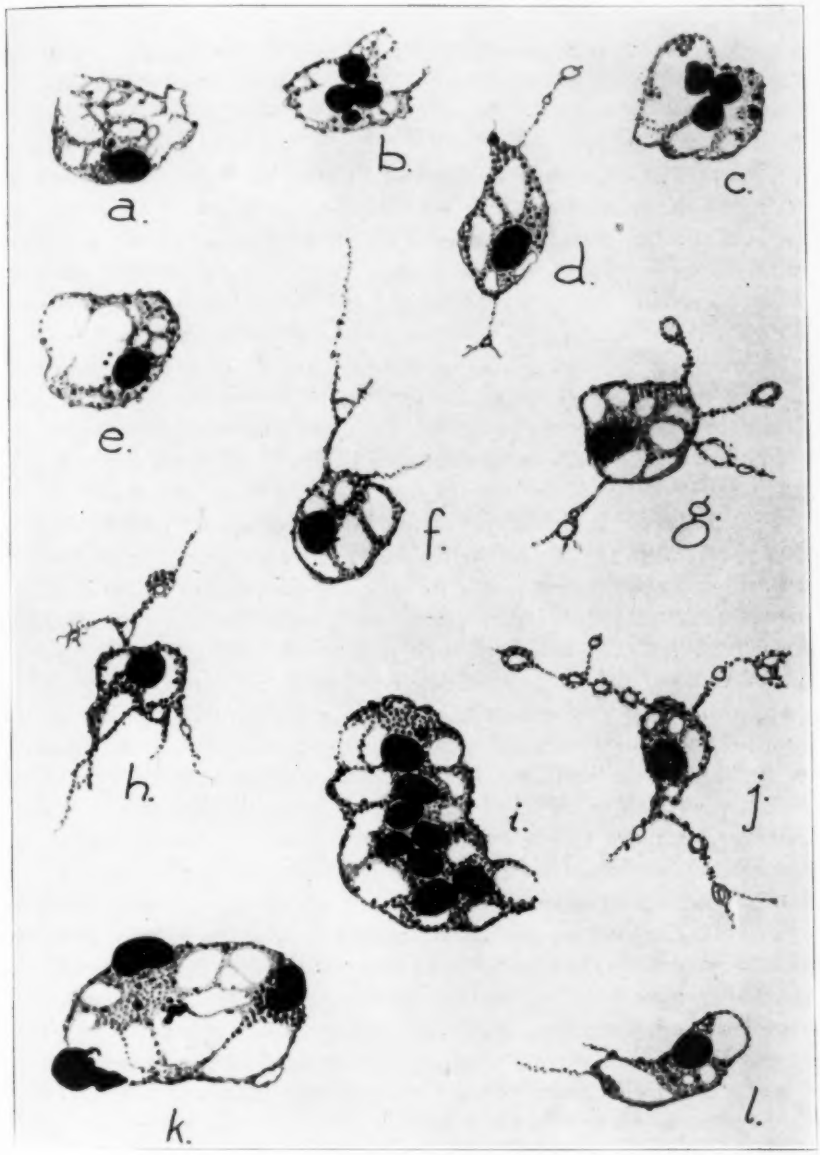

Fig. 12.—Transitional and atypical forms of oligodendroglia in acute swelling: *a*, protrusion of one portion of the cell wall, rupture of a large vacuole; *b* and *c*, multinucleated cells, note the polar body in *b*; *d*, elongated form with an expansion on either end; *e*, rupture of intervacuolar septum; *f* and *g*, early forms with expansions still present; *h*, macelike swelling of process; *i* and *k*, fusion forms; *j*, beadlike appearance of process due to the formation of vacuoles; *l*, "peanut" or "comma" form.

sions, the cells finally assume a round or slightly oval shape. This is usually found in the form of acute swelling, characterized by a "wire wheel" appearance, a dark central nucleus, a narrow granular rim and "spokes" of protoplasmic girders. At this stage the cell has become tremendously enlarged. Some of the peculiar types are shown in figure 12.

Regressive changes give the cell in turn an irregular appearance, owing to the rupture of large vacuoles and the breaking up of the cell membrane with loss of substance. This will be discussed in more detail later. Finally, one occasionally sees very large, unbroken rings of miliary vacuoles and granules which enclose neither nucleus nor cytoplasm. Whether these forms represent tremendously swollen cells in which the nucleus and cytoplasm have undergone destruction and solution, or have been extended by rupture of the membrane in another plane, has not been determined. It is, of course, possible that the pyknotic nucleus has become eccentrically placed and does not appear in this section.

The process of vacuole formation in the cell merits further description. It is a universal process involving the expansions, as well as the cell body. In the former it usually occurs at the point of bifurcation, but it may be found in the form of small or moderately sized vacuoles along the course of the process itself. In some instances, the usually approximated walls of the process are separated by a fusiform vacuole, in the margin of which small secondary vacuoles and granules are to be found. In some of the processes, the vacuoles are eccentrically placed, appearing as small yeastlike buddings. In rare instances, a process may appear diffusely swollen, with fine granulation of the cytoplasm; this change, however, is more characteristic of microglia. In the cell body the vacuoles show a variation in size and location, assuming either a peripheral or a central situation. In the former, small vacuoles may be found adjacent to the nucleus or the cell membrane, where they may appear in rows or chains. When the process of acute swelling is fairly rapid, the entire cell may be filled with a greater or smaller number of large vacuoles of uniform size. If the process is even more rapid, there may by a coalescence of several vacuoles, giving rise to large ragged cystlike spaces. Such changes favor the destruction of the cell. These large vacuoles are prone to rupture through the cell membrane, with a resultant loss of portions of this structure. Smaller vacuoles, however, may also rupture externally. The cytoplasm may be packed with numerous small vacuoles, giving it a lacelike appearance. At times, more peripherally situated vacuoles may rapidly enlarge, causing a local bulging in the cell wall. When viewed under highly corrected lenses, it appears as though the cell membrane itself is vacuolated. In such cases, along with granulations, small miliary vacuoles seem to occur within the membrane itself.

One unusual type of vacuolization in what are presumably oligodendroglia has been observed. In cases in which the process of acute swelling appears to be rather marked, cells are occasionally found that are filled with a single large vacuole. The finely granular cytoplasm has been compressed into a peripheral crescent. The small dark nucleus usually occupies the midpoint of the crescent, but may be found partially or wholly extruded from the cell. The cell wall is extremely thin, and in some situations is indicated only by a row of granules. Rupture of the large single vacuole frequently occurs. We have designated these cells as "signet ring" forms. They were especially conspicuous in case 13.

The nucleus itself undergoes certain alterations as a result of vacuole formation. It may be distorted by closely approximated external vacuoles resulting in comma, horseshoe or gourd-shaped forms. The nuclear substance itself may be occupied by one or more vacuoles, which may be bilobed, dumb-bell or trefoil shaped, or may appear as a single, fairly large, round fluid space. Again, coalescence of many small vacuoles may result in peculiar irregular maplike patterns within the nucleus. These may gain access to the nucleus by indentation of its membrane or by diffusion through it.

One of the first indications of change in the cytoplasm is an enlargement of the hitherto fine granules. The slightly swollen cell may be completely packed with these large granules. They become separated and irregularly distributed as the vacuoles increase in number and size, and assume a peripheral or perinuclear situation. The large irregular masses occasionally found in the cytoplasm are probably formed by a coalescence of these granules. When they become adherent to the nuclear wall, they give it a rather nodular appearance, often accentuated by the presence of a clear zone or halo, which separates it from the cytoplasm of the cell.

Cell Division.—Proliferation of the oligodendroglia takes place largely, if not entirely, by direct cell division (fig. 13). As has already been mentioned, cell division begins within the first few hours after injury and continues for variable periods as long as existing circumstances demand. At the end of two hours (case 3), two, three or even four nuclei were repeatedly found within a single cell. Cell division begins by a constriction in the nucleus which usually divides into two equal parts, with the final appearance of an intervening membrane separating the two daughter cells. At times one of the two or more nuclei may be smaller than the others, appearing like a polar body, a condition similar to that occasionally seen in the microglia. An elongated nucleus may divide into two or more longitudinally placed nuclei. On the other hand, irregular division of a single nucleus may result in a clump of centrally placed daughter nuclei. We have failed to see mitotic cell division of

the oligodendroglia in this series of cases. In nuclei undergoing direct cell division, the chromatin granules which are usually centrally placed, often assume a more peripheral location and are inclined to adhere to the nuclear membrane. This may be a provision to ensure equal division of the chromatin substance in the two daughter cells.

Fusion Forms.—As has already been described by other observers, particularly Ferraro and Davidoff,[32] fusion forms of oligodendroglia seem to be fairly common. They appear within the first few hours following injury to the brain. They are characterized by an agglutination of a row or clump of adjacent cells, often with a loss of separating cell

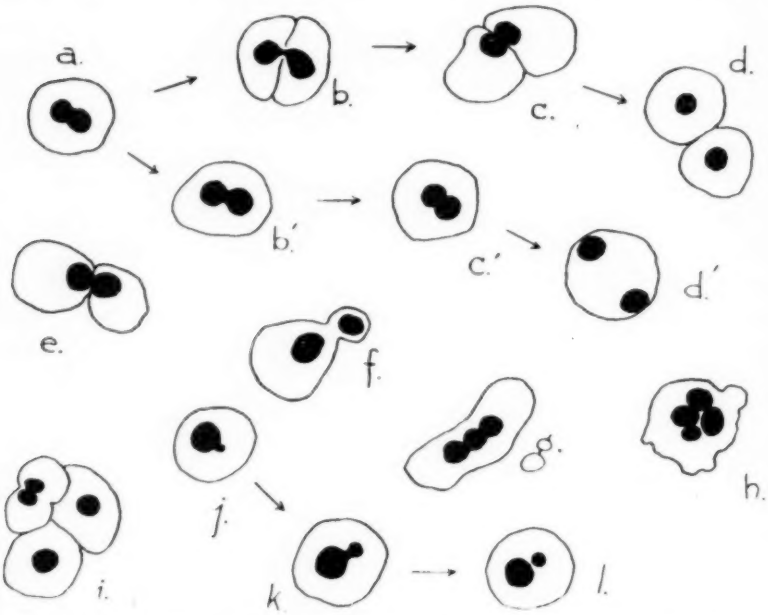

Fig. 13.—Modes of cell division in oligodendroglia: *a* to *d*, simple, direct cell division; *a* to *d'*, division of the nucleus without division of the cell cytoplasm; *e*, longitudinal cell division; *f*, unequal cell division; *g* and *h*, multinuclear cells; *i*, cell division in fusion form; *j*, *k* and *l*, "polar body formation."

membrane. These fusion forms may appear as a fairly even row of nuclei, apparently resulting from the fusion of interfascicular cells. They may also appear as a clump of nuclei surrounded by an irregular wall from which they are separated by vacuoles of various sizes. It is often difficult to be certain whether a given multinucleated form is the result of direct cell division or whether it is a true fusion form. In some cases, it seems fairly evident that such structures are in fact a combination of both, some of the individual nuclei dividing after fusion has taken place. The cause of fusion is not clear. The tendency for the

nuclei to agglutinate and become pyknotic along with active degeneration of portions of the fused cytoplasm may indicate the first stage in a regressive change. It may be due to an attempt on the part of a group of cells to react as a unit against an overwhelming noxious process.

Regressive Changes.—As has already been described by Penfield and Cone,[31] alterations taking place in this type of cell may constitute a reversible process. If the injury or insult is not too profound, they are capable of returning to their original state. In other words, there is a process of necrobiosis, which, if continued, leads to cell destruction. In cells undergoing rapid swelling, such changes are first manifested by the

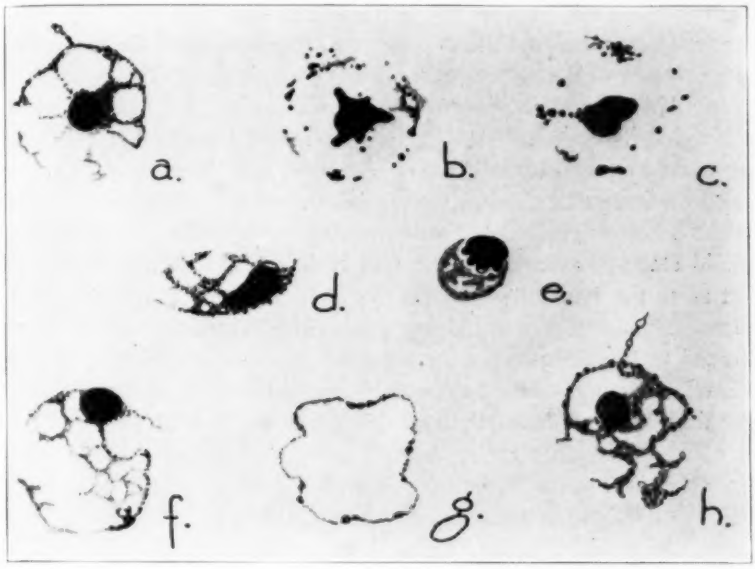

Fig. 14.—Regressive changes in oligodendroglia: *a*, destruction of one portion of cell; *b* and *c*, granulation of the cytoplasm with pyknosis; *d*, nucleus and perinuclear cytoplasm of partially destroyed cell; *e*, shrunken cell with perinuclear halo; *f*, multiple ruptures of large vacuoles bringing about destruction of the cell; *g*, ring form without nucleus; *h*, coarse granulation and disintegration of one portion of the cell.

occurrence of ragged cell spaces or rupture of the cell wall. Extensive rupture may even result in loss of cell substance and, in some cases, in extrusion of the nucleus. Pyknosis and vacuolization of the nucleus are possibly early manifestations of regressive change. In regions immediately adjacent to lacerations or severe contusions, destruction of the oligodendroglia occurs much in the same way as in the microglia, that is, by solution of the cell membrane, the formation of heavy granules or "explosion" of the cell body. In these situations they share the common

fate of all other cellular elements. Some of the regressive changes are indicated in figure 14.

The Formation of Compound Granular Corpuscles from Oligodendroglia.—In their study of experimental brain injury, Ferraro and Davidoff [32] came to the conclusion that oligodendroglia as well as microglia take part in the formation of compound granular corpuscles. This is a new conception, for since the introduction of specific methods, practically every observer has agreed that typical compound granular corpuscles are formed from microglia or connective tissue elements. From the results of our study on human material, we are unable to support this conception of Ferraro and Davidoff, even after combining the specific method with that of the demonstration of fat which they suggest. There are several reasons that seem to us to controvert their conclusion. First, there is only one stage in which the changing oligodendroglia at all resemble transitional stages of the microglia. This is the one previously described as the stage characterized by some swelling of the expansions and asymmetric vacuolization of the cytoplasm, which give the cell an irregular shape. On occasion one might be in doubt for a moment whether such a cell was a changing oligodendroglia or a preameboid stage of microglia. Careful study, however, usually leaves no doubt as to the true nature of the cell. In no other instance was there the least confusion, nor could any transitional forms of oligodendroglia be traced to the formation of compound granular corpuscles. Furthermore, while one must admit the possibility that individual oligodendroglia might undergo a form of lipoidal degeneration, such as is found in the case of ameboid glia, cells undergoing this change have never come to our attention. Finally, in areas in which the active formation of compound granular corpuscles was taking place, oligodendroglia were conspicuous by their absence. The former difficulty in distinguishing transitional forms of microglia from degenerating neuroglia is now largely done away with by the introduction of specific methods, and need not occupy attention further in this connection.

The Rôle Played by Oligodendroglia in Injury to the Brain.—It is believed by those who are best informed that during later embryonic life and infancy, the oligodendroglia play an active rôle in the formation of myelin sheaths. This is suggested by the rapid development of the oligodendroglia and the presence of large gliosomes in their cytoplasm during the period of active myelinization of nerve fibers in the central nervous system. Furthermore, their position between the nerve fibers in the white substance makes them a counterpart of the sheath cells in the peripheral nerves. That such cells have an additional protective function is suggested by the position of the perineuronal satellites. We have seen that the oligodendroglia have, in the main, a generalized reaction in con-

trast to the microglia the response of which is localized to areas of damaged brain. At the outset, this fact would indicate that, while there may be some minor overlapping of their function, each element has a specific part to carry out in the reaction of the brain to injury. It is, furthermore, recognized from our observations that acute swelling of the oligodendroglia resembles closely that observed by Penfield and Cone [31] and others in general toxic states. It is evident that no generalized toxemia exists in cases of cerebral injury, and that one must look elsewhere for an explanation of this phenomenon. It is furthermore accepted that the only generalized change that occurs in these cases is that of cerebral edema, presumably of vascular origin. As has already been shown in the case of the choroid plexus and ependyma, and we trust will be demonstrated in the neuroglia and neurons, this process involves practically every element in the central nervous system. Vacuolization is found in the epithelium of the choroid plexus and ependyma, the nerve cells and glia cells, particularly in the nuclei of the latter. It seems to us that acute swelling of the oligodendroglia in injury to the brain is one manifestation of a diffuse edematous process. This cellular edema is very likely a mechanical factor in the production of swelling of the brain. Other factors may play a part in its production, but at present they are unrecognized.

SUMMARY AND CONCLUSIONS

In studying histologic changes in the human brain consequent to injury, we have utilized the newer metallic methods, as well as routine stains. In this contribution we have limited ourselves to a consideration of the microglia and oligodendroglia. The history of these two elements has been briefly traced, with special reference to more recent studies with specific metallic methods. To the present time the reaction of these elements to injury has been critically studied only in experimental animals. In this investigation we have attempted to follow the changes in the microglia and oligodendroglia in cases of fatal injuries to the human brain. We have selected twenty-four cases from a larger series which represent fairly typically the sequence of changes occurring in edema, contusion and laceration and gross and petechial hemorrhages of the brain.

The microglia react to local destruction and disintegration of tissue. The oligodendroglia, on the contrary, are altered in response to general or widespread processes, particularly edema. Transitional forms of microglia were found within the first few hours following contusion or laceration of the brain. Compound granular corpuscles, however, were found only after three or four days, and remained as long as the products of disintegration were present. Typical transitional stages could be traced from normal microglia to fully developed phagocytes. The

oligodendroglia became enlarged and vacuolated almost immediately following injury. Within a few hours, typical widespread acute swelling of the cells was present. This reaction undoubtedly persists for weeks, especially in the region about local injuries. Both types of cells undergo destruction along with the nerve cells and neuroglia, at the margin of lacerations and in severely contused areas. Evidences of direct cell division were observed in both types of cells within a few hours after injury, and it was especially active during the first few days. Mitosis was found only in fully developed compound granular corpuscles.

Changes in the astrocytes and nerve cells will be described in later communications.

FAMILIAL PROGRESSIVE MUSCULAR ATROPHY*

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WITH A PATHOLOGICO-ANATOMIC STUDY BY W. C. JOHNSON, M.D.,

AND

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DENVER

Chronic progressive wasting of the skeletal muscles as a clinical observation has claimed the attention and interest of neurologic observers for many years. The underlying cause is a subject regarding which opinions have varied considerably from time to time. Since the christening of the disease by Aran, several types have been withdrawn from the original group, leaving a small and comparatively rare entity to which the name progressive muscular atrophy may still appropriately be applied.

Several clinical conditions in which muscular atrophy occurred as an incidental accompaniment rather than as a primary dominant characteristic—such as syringomyelia and unusual or aberrant forms of disseminated sclerosis—were withdrawn from this classification and, later, the subacute and chronic forms of poliomyelitis, the primary myopathies and some of the chronic or toxic forms of peripheral neuritis were eliminated, leaving the original term to represent what may now be regarded as an exceedingly rare disease.

Opinions still differ as to whether sufficient variation exists between the types of muscular wasting to justify the distinction, and the propriety of the separation of some types from the inclusive heading, under which all forms of muscular atrophy originating in the spinal cord are grouped, is questioned. This appears to be especially true with reference to the diseases individually recognized as subacute and chronic anterior poliomyelitis, amyotrophic lateral sclerosis and progressive diffuse degeneration of the spinal gray matter or progressive muscular atrophy.

It is interesting to observe, however, that cases in which the white

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* From the Departments of Neurology and Pathology, University of Colorado.

matter has remained unchanged are encountered, notwithstanding the prevailing opinions to the contrary. Williamson [1] stated:

> The white matter of the cord may be unaffected; but often there is atrophy of the fibers in the anterolateral columns just adjacent to the anterior horns. These are commissural fibers and the slight degeneration at this region has occasionally the appearance of a crescent-shaped zone around the anterior horns. The degenerated fibers are anterior to the crossed pyramidal tracts. In true cases of progressive muscular atrophy the crossed pyramidal tracts are quite normal in appearance.

The similarity of the clinical picture presented by peripheral multiple neuritis and progressive muscular atrophy was again emphasized by a recent study,[2] which recalls the cases reported by Grinker [3] in 1907, in which he stated:

> It is well to remember that cases of progressive muscular atrophy of spinal type are rather rare and that pathologic examination has proved many a case of supposed spinal atrophy to be neuritis.

Finally, on the strength of the observations of Strümpell, Pick, Abundo, Cassirer, Haushalter, Cohn, K. Mendel and others, Oppenheim [4] drew the following conclusion:

> Not a few cases have been described which, from their clinical features, appear to be related as well to the spinal as to the myopathic and the neurotic forms of progressive muscular atrophy, and can be completely included neither in the one nor the other group.

It has been stated that in progressive muscular atrophy the muscles are affected according to their physiologic grouping in the cord, while in peripheral neuritis they are affected according to their innervation, regardless of segmental grouping. This distinction, however, would seem to be much more pronounced in the poliomyelitic types.

In view of the many conflicting observations, especially with reference to diseases of the peripheral neurons of subacute or chronic evolution without implication of the pyramidal pathways in the cord, the term progressive muscular atrophy finds a justification in that it expresses the dominant clinical state.

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1. Williamson, R. T.: Diseases of the Spinal Cord, New York, Oxford University Press, 1908, p. 235.

2. Hyland, Herbert H., and Russell, W. Ritchie: Chronic Progressive Polyneuritis, with Report of a Fatal Case, Brain **53**:278, 1930.

3. Grinker, J.: Multiple Neuritis Simulating Progressive Muscular Atrophy, J. A. M. A. **48**:849 (March 9) 1907.

4. Oppenheim: Text Book of Nervous Diseases, translated by Bruce, Edinburgh, Otto Schulze & Co., 1911, p. 236.

The case to be reported is presented as one of progressive muscular atrophy. It is believed to be distinctive in that: (1) The patient was followed for over twenty-one years and apparently an identical condition was present in two of his brothers observed at the same

Fig. 1.—Three brothers, showing different degrees of the same type of generalized atrophy in 1907.

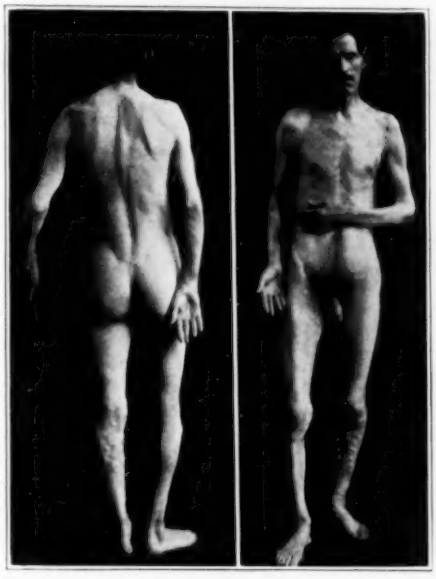

Fig. 2.—The patient in 1907, showing the early appearance of the wasting.

time; (2) while the pronounced weakness and wasting were first noted in the hands and arms, the extreme wasting of the hands with the claw-like deformity, or main en griffe of French writers, was not present even though the eminences were markedly wasted and the power was reduced to a minimum.

In evidence of the uniform involvement was an interesting observation of the three brothers while at breakfast one morning in about the year 1912. The pot of coffee was handled with great difficulty and required the effort of two of the brothers, while only the soft inner portion of the bread could be eaten because the weakness of the jaw muscles precluded the mastication of the outer crusts.

The same uniformity in muscular weakness was present in all three brothers. The tendon reflexes were gradually diminished, but were distinctly elicited during life. No pain or disturbance in sense perception was observed. There was no involvement of the cranial nerves

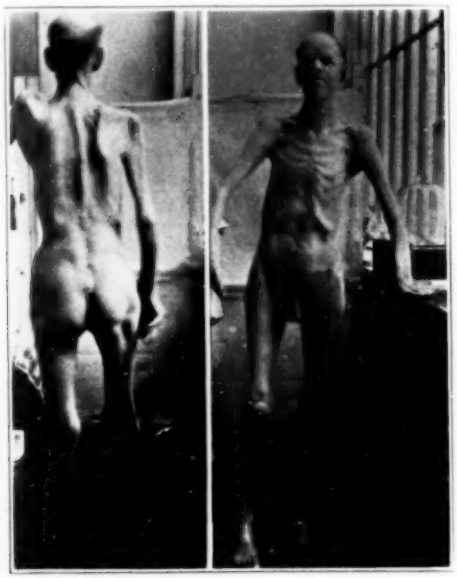

Fig. 3.—Brother of the patient, as he appears at the time of this report.

other than the motor supply of the trigeminus and the hypoglossal nerves. An advanced pyorrheal infection of the teeth was present in all of the brothers when they were first seen.

The cause of death of the oldest brother, which occurred in my absence, was stated in the hospital record as myocarditis and auricular fibrillation; the second brother died apparently of complete exhaustion; the third is still living at the time of this report and presents an advanced state of the disease, as is evident from the pictures presented herewith.

REPORT OF CASE

History.—L. B. L., who was first seen on Nov. 5, 1907, at the age of 35, had been occupied as a cement finisher until the weakness in the hands had become so marked as to preclude continuance. The mother was living and in good health.

The father had died of pneumonia. One brother was said to have died of lead poisoning; another could not walk because of weakness in the legs, and a third brother presented distinct evidences of a similar muscular disease. A sister had died of goiter. One brother was living in good health, and the whereabouts and condition of another were unknown. No other constitutional, nervous or mental diseases had occurred in the family.

The patient was the third child born in a family of seven. He had had measles and whooping cough in childhood. He was in good health until the age of 21, when he had typhoid fever, following which he was weak for four months. In 1895, he had grip, after which he was well until manifestations of the present condition appeared, in about 1899. He said that he had not had chancre or other manifestations of syphilis or gonorrheal infection. Alcoholic indulgence was limited to an occasional glass of beer. He stated that the only time he had ever drunk to excess was thirteen years prior to examination. He smoked considerably, usually a pipe.

About 1899, while on a ranch, the patient began to notice loss of power in the hands and arms, which became progressively weaker and thinner; this weakness was more pronounced on the right side, having been noticed first in the right hand. After about four years, weakness in the legs became evident, first on the right side. This likewise had progressed steadily. No numbness or tingling was noticed at any time, nor was there any pain. There had been no difficulty in the control of the bladder and bowels. Occasional dizziness, accompanied by "palpitation of the heart," had been experienced, especially when stooping. The difficulty in walking had increased gradually. An occasional twitching of the muscles was noticed. There had been no subjective difficulty of vision, either as diplopia or amblyopia. There had been no headache or vomiting without recognizable cause. The appetite had been fair; the bowels were regular, and sleep had always been good.

Examination.—The patient was an anemic, slender white man, 6 feet, 1 inch (185.4 cm.) in height, who weighed 147 pounds (66.7 Kg.). His replies were responsive, without evident speech defect, and his memory was good. There was wasting throughout the body, somewhat more evident in the hands, arms and shoulders than elsewhere. The tongue was protruded in the middle line; it was slightly tremulous and shriveled, and the volume was reduced. The brows wrinkled equally, and the mouth retracted evenly. There was no tremor of the hands. Muscular power in the grasp was greatly reduced (dynamometer readings [Tiemann, inner scale] were right, 15 and left, 15). The flexor and extensor power in the arms was markedly diminished. The finer movements of the fingers were much impaired, more so in the left hand, with which the patient was unable to pick up a pin. He could not button his clothing with either hand alone. The wasting appeared to be symmetrical in all muscles of the arms, forearms and hands, as well as in the shoulders, but it was particularly evident in the hands. The thenar and hypothenar eminences were distinctly wasted, as were all the intrinsic muscles. No spontaneous fibrillation was noted, but tapping the pectoral muscle caused a rhythmic wavelike contraction from insertion to origin. There was only slight fibrillary response, and at times there was some tremor of the hands. In walking the patient raised the feet higher than is normal in order to clear the toe; the foot was carried forward and struck the floor flat. The left foot was considerably less secure than the right; this was more noticeable when the patient's eyes were closed. There was no ataxia evident in the muscles of the arm or trunk.

Electrical Reactions: Faradic irritability was prompt. Results obtained with the galvanic current follow (figures indicate milliamperes). Biceps: Cathodal closure current, right, 11 (28 caused tetany) and left, 8+; anodal closure current, right, 29 and left, 12; cathodal opening current, right, no response with the strongest current, and left, 20; anodal opening current, no response with the strongest current. Triceps: cathodal closure current, right, 5, and left, no response at 8; cathodal opening current, right, no response at 25. Deltoid: right and left, cathodal closure current, 8.

Reflexes: The knee jerks were slight, but were increased on reenforcement; ankle clonus was absent; the achilles jerk was slight or absent on the right, present on the left; the deep reflexes of the forearms were greatly diminished; a pectoralis major response was present on both sides; the biceps was more active than the triceps jerk, equally on the two sides; the deltoid reaction was slight or absent; the masseter and jaw jerk were absent. The plantar reflexes were active, flexor and equal on the two sides; the lower abdominal and epigastric reflexes were active; the ciliospinal reflex was present on both sides.

Sensation: All forms of sense perception, including those of touch, stereognosis, pain, temperature, posture and localization, were present and equally prompt throughout.

Eyes: All external ocular movements were present, equal and without nystgamus. The pupils were approximately 2.5 mm. in diameter, and responded actively to light and distance and slightly on convergence. The fields of vision were normal to finger testing. Vision was 6/6 in both eyes. There was no change in the ocular fundi; the disks were slightly hyperemic, but this was attributed to strain; a refraction test showed hyperopia of 1 diopter; when corrected the visual acuity was 6/5.

Ears: A 24-inch watch was heard at a distance of 24 inches on the right and 26 inches on the left. A tuning fork was heard best in the closed ear. Air conduction was greater than bone (right, 4:1; left, 3:1).

Course.—On Feb. 13, 1908, the gait was more unsteady, and the legs, which were raised voluntarily owing to the frequency of stubbing the toes, were lifted higher on account of the difficulty in clearing the toes. The patient was able to stand on the tips of the toes, but was unable to raise the toes and stand on the heels, the strength in the anterior tibial group of muscles being markedly diminished on both sides as compared with the posterior ones. The power of the extensors of the hands was notably less than that of the flexors.

On Sept. 3, 1911, the patient complained of ease of tiring. He had a subjective sense of cramping with the inauguration of a movement; some twitching had been noted. Muscular power had gradually lessened. The weight had been reduced to 142 pounds (64.4 Kg.). There was an increase in weakness of the grasp. No pain was experienced in any part of the body. A slight difficulty in articulate speech was recognized, especially in cold weather, when the patient stated that the muscles of the tongue would not move as well as before. There was slight difficulty in swallowing unless the head was held in the upright position; on attempting to drink while in a horizontal position, the water ran out of the nose, and if he drank hurriedly he invariably strangled. There had been no sphincter disturbances, numbness or tingling. The eyesight and hearing were unchanged.

At this time there was a uniform loss of power. The movements of the head were notably weakened, and it had often been necessary for him to assist with his hand when raising his head from the pillow. The sternocleidomastoids acted fairly well. The depressors of the jaw were weak, and the temporal, pterygoid

and masseter muscles were markedly weakened. When the jaw was depressed the condyles were easily dislocated forward on the eminentia articularis. Wasting of the temporal muscles was marked. Flexion of the forearms was not so weakened as extension, and the disparity was even more marked in flexion and extension of the hands. The intrinsic muscles of the hands showed more wasting than before, and the eminences were less prominent, more so on the right than on the left; dynamometer readings were: right, 20; left, 10.

The predominance of strength in the flexors was further evident in the grasping of objects; the patient found difficulty in relaxing the grasp, the extensors being too weak to overcome the contraction of the flexors which, on fixation in a hyperextended position, became markedly contracted. Supination was weaker than pronation in the left arm, but about equal in the right. The supinator longus was obviously more wasted in the left arm. Flexion and extension of the thigh were about equal. Flexion of the leg was performed with greater power than extension. Dorsiflexion of the feet was accomplished only with difficulty and, when dependent, the feet hung in a position of plantar flexion, or foot drop. The right lower extremity was weaker than the left; both were markedly wasted, but no paralysis of muscles or groups was detected. The peroneal and posterior tibial groups responded to a strong faradic current, but, with the galvanic, up to 24 milliamperes, no contraction was elicited in either group. Tapping the quadriceps or sartorius caused a myotatic response. The abdominal recti muscles contracted but showed much weakness when the patient attempted to raise his head while in the dorsal position; this movement could not be accomplished without the aid of the hands.

The knee jerks were present only on reenforcement; ankle clonus was absent; the achilles jerks were absent; tapping the right forearm extensor tendon caused a slight extension of the fingers, which slowly relaxed; the flexor response was more prompt; the right supinator jerk was slight, the left absent; the biceps, triceps and deltoid jerks were feebly responsive; the masseter jerks were absent; the jaw jerk was slight. The plantar reflexes were of flexor type; the Oppenheim test caused slight flexion on both sides; the compression of the calf (Gordon) caused no response on the right and slight flexion on the left; the cremaster reflexes were present; the abdominal and epigastric reflexes were equally present; the ciliospinal reflex was present bilaterally.

All forms of sense perception, including stereognostic sense, were prompt and equal on the two sides.

The external ocular movements were equal, normal and without nystagmus; the pupils, 2.5 mm. in width, were equal and responsive to light and in accommodation. Both eyes were hyperopic and required about +2 diopters. The vessels of the fundus were somewhat attenuated and there was slight haziness of the disks. Vision was 15/20 on the right and 15/30 on the left. Hearing was diminished to 8/24 in both ears. A tuning fork was heard best in the closed ear; air was greater than bone conduction (right, 2:1; left, 2.5:1). Taste was conducted very slowly; quinine placed on the tongue was perceived several minutes later and salt, after three or four minutes. Some diminution was noted on the pharyngeal wall. Smell was fairly prompt and accurate on both sides.

The blood pressure was 122 systolic and 92 diastolic; hemoglobin measured 78 per cent.

In 1926, the patient was admitted to the Denver General Hospital, with a slight injury to the left tibia, the result of a fall. Four years previously, the same bone had been fractured in a fall. The legs at this time showed considerable lividity when dependent. Examination of the blood revealed 9,450 leukocytes (poly-

morphonuclears, 68 per cent; lymphocytes, 32 per cent). Urinalysis revealed a trace of albumin and no sugar, acetone or indican; the sediment contained a few pus cells. The Wassermann reaction of the blood was negative.

In 1928, the patient attempted suicide by cutting the wrists, explaining that he recognized the progress of the weakness and helplessness. No paralysis was present in any part of the body, but after slight movement the fatigue was so profound as to require rest before a fresh attempt. It required the greatest effort for the patient to swallow 3 ounces of fluid.

Death occurred on Oct. 17, 1928, twenty-one years after the patient was first seen and about twenty-nine years after the first manifestation of the disease. Death was regarded as due to complete exhaustion. The body temperature between July 21 and October 17 ranged between 96.8 and 98.6 F., except for one rise to 99.8 F. for a few hours. At the time of death it was 98 F.; the pulse rate was 80, and the respirations 20 until death.

Examination of the blood on July 22, 1928, had shown: leukocytes, 7,200 (polymorphonuclears, 67 per cent; lymphocytes, 31 per cent; eosinophils, 1 per cent; transitionals, 1 per cent). Urinalysis revealed no albumin, sugar, acetone or indican; microscopically, a few pus cells and mucus were found. The Wassermann reaction of the blood was negative.

Necropsy (Oct. 18, 1928, twenty-one hours post mortem).—The anatomic diagnosis (Dr. W. C. Johnson) was: (1) generalized muscular atrophy of the skeletal muscles; (2) emaciation; (3) bronchopneumonia; (4) fibrous scars of the apex of the left lung; (5) brown atrophy of the liver; (6) atrophy of the spleen; (7) atrophy of the testes, with hyperplasia of the interstitial cells; (8) atrophy and fibrosis of the appendix; (9) osteoporosis of the ribs; (10) fibroma of the right kidney, and (11) small colloid cyst of the thyroid.

There was moderate edema of the pia-arachnoid. The brain weighed 1,390 Gm.; it showed no definite gross lesions. The spinal cord in the cervical enlargement appeared practically normal; the lumbar region felt soft and flabby, and appeared shrunken.

The tongue was small, wrinkled and thin. The esophageal wall was thin, especially at the upper end in the region of the voluntary muscles. The diaphragm was thin and pale. The muscles of the arms, thighs and calves were extremely wasted and very pale; the fascia was condensed and loose around them. Some of the muscles were so shrunken that they were hard to identify. The condition appeared to be fairly uniform throughout the upper and lower extremities. The muscles of the anterior abdominal wall were much better preserved and showed an almost normal color; the muscles of the lumbar region of the back were in a fair state of preservation.

Several of the peripheral nerves in the extremities appeared normal grossly.

Microscopic Studies (Dr. W. C. Johnson): For a study of the muscles the methods used were: hematoxylin and eosin stains of tissue fixed in a diluted solution of formaldehyde, U. S. P. (1:10) and embedded in paraffin, and frozen sections stained with hematoxylin and scarlet red. Measurements of the fibers were made from the paraffin sections. There were sections from eight muscles. In general, the different muscles showed degrees of atrophy varying from slight to complete (fig. 4*A*). In each individual muscle the fibers also varied in size, some showing more marked atrophy than others.

From a comparison of fibers in different stages of atrophy, the development of the lesion appears to be as follows: There is first a narrowing of the fibers, without noticeable change in the nuclei or striations. The striations persist until

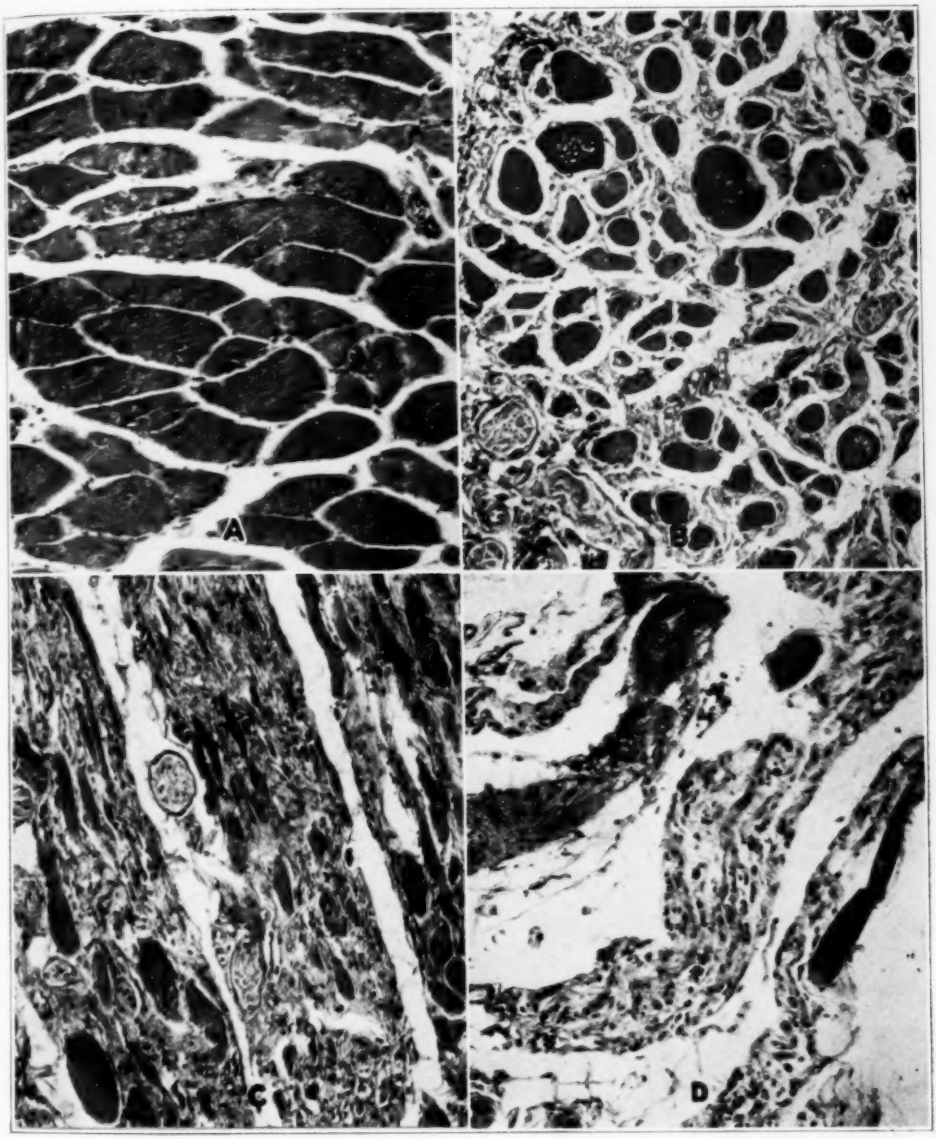

Fig. 4.—Photomicrographs at the same magnification (× 110), showing different degrees of atrophy in striated muscles: *A*, right psoas major; *B*, diaphragm; *C*, right temporal, and *D*, right vastus medius.

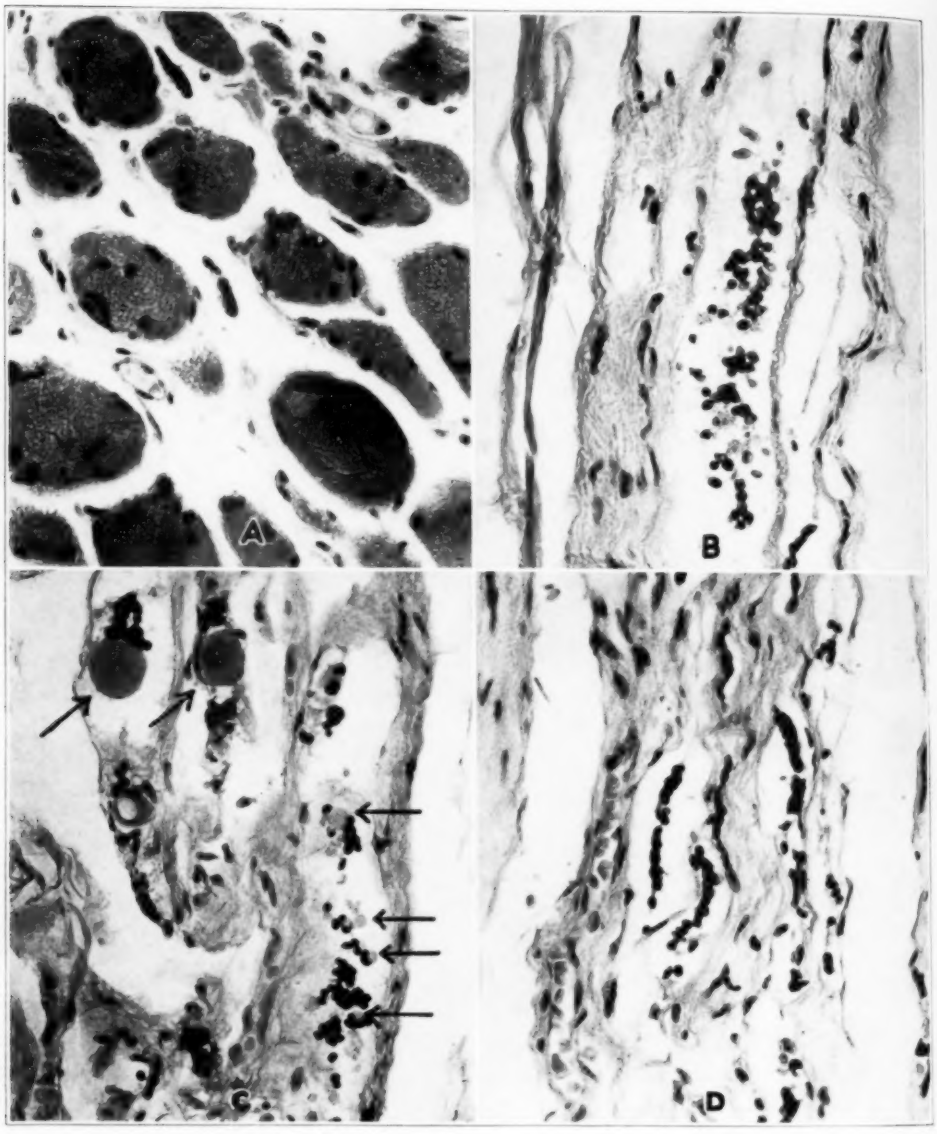

Fig. 5.—Photomicrographs (× 300) showing changes in striated muscle fibers: *A*, sinking of nuclei into muscle fiber (right biceps brachii); *B*, large clump of nuclei in atrophied fiber (left gastrocnemius); *C*, hyaline bodies (corpora amylacea) in atrophied fibers (left gastrocnemius), and *D*, chains of nuclei in atrophied fibers (left gastrocnemius).

the fiber has become very narrow. Finally, the cross-striations disappear, but longitudinal striations are apparent for some time longer. The muscle substance later shrinks to a pale wavy strand without striation. At first, the sarcolemma shrinks with the fiber, but in the late stages the shrinkage of muscle substance leaves an apparently empty space between it and the sarcolemma. Later, small, round hyaline masses resembling corpora amylacea appear along the course of the narrow strands of muscle substance. A small amount of granular material and the hyaline masses are the last remains of the muscle substance seen before its complete disappearance (fig. 5 *C*). Some of the fibers contain a few granules of yellowish pigment resembling a lipochrome.

The nuclei of the fibers show no noticeable changes in the early stages of atrophy, except that some of the nuclei lie in the interior of the bundles (fig. 5 *A*). In the later stages, they are apparently more numerous and closer together, but whether this is due to condensation or actual proliferation cannot be definitely determined; they appear too numerous for it to be due to condensation alone. The nuclei at first are oval rather than elongated; later they become small, round and pyknotic, resembling the nuclei of lymphocytes. In this stage they are clumped in small, compact clusters along the remaining strands of muscle substance and around the small hyaline masses. Frequently, the nuclei are arranged close together in a row along the remains of the fiber like a string of black beads (fig. 5 *D*). The nuclei persist after all trace of muscle substance has disappeared, and are then seen lying in narrow and otherwise apparently empty spaces enclosed by sarcolemma. In cross-sections of the fibers the nuclei lie in clusters in the centers of empty spaces, resembling fat cells. Later, the spaces around them diminish, and finally the last stage that can be recognized is represented by a number of nuclei lying in wavy bundles of what appears to be merely connective tissue fibers (fig. 5 *B*).

With the atrophy of the fibers the sarcolemma does not appear to be thickened, nor is there any increase of interstitial connective tissue. There is no infiltration of the interstitial tissue with cells that might indicate an inflammatory reaction, nor is there any evidence of invasion by phagocytic mononuclear cells. There is no definite evidence of necrosis of the fibers, and no hypertrophy or marked replacement by adipose tissue such as may be seen in pseudohypertrophic muscular dystrophy. Adipose tissue is present between many of the muscle fibers, especially in those of the extremities, but it does not appear to be more than relatively increased, although a section of the gastrocnemius is composed of practically nothing but fat.

Fat stains show the fibers in the best preserved muscles to be filled with very fine droplets, uniformly distributed through the fibers. Individual fibers vary considerably, some containing much more fat than others. With the atrophy of the fibers there appears to be a decrease rather than an increase in fat, although they contain a few droplets even when the atrophy is far advanced.

The muscles examined, listed in order of the degree of atrophy shown, with the best preserved first, are: (1) Psoas major. The fibers were all well preserved and varied from 30 to 90 microns in diameter. None showed any marked atrophy (fig. 4 *A*). (2) Right rectus abdominis. Most of the fibers were well preserved, and measured from 30 to 100 microns in diameter. A few appeared atrophied and measured from 10 to 20 microns in thickness. (3) Diaphragm. The fibers varied considerably in size, measuring from 10 to 90 microns, most of them being from 30 to 40. None had reached any advanced stage of atrophy, although there were some from 10 to 20 microns in thickness (fig. 4 *B*). (4) Right sacrospinalis. The fibers varied markedly in thickness, the largest showing a mean dia-

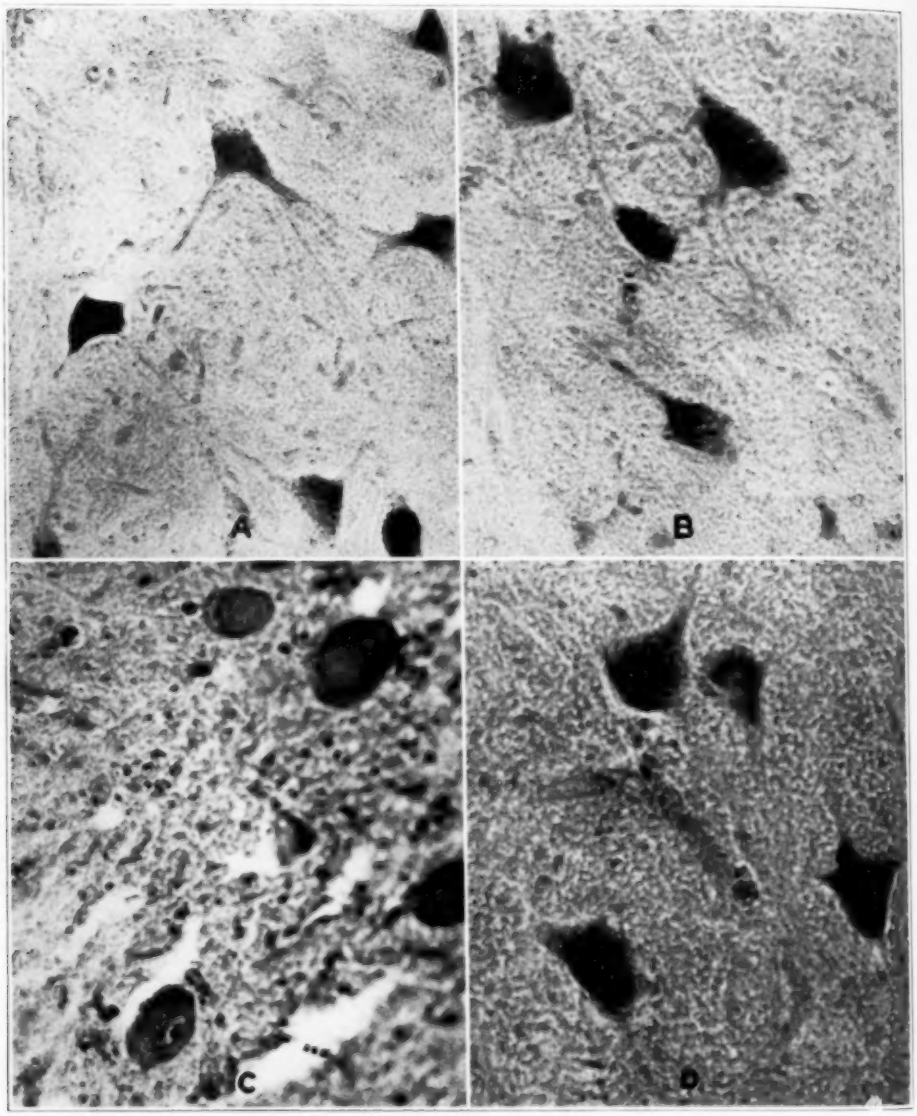

Fig. 6.—*A*, normal number and distribution of cells in cervical enlargement and anterior horn. The cells are still intact and have a normal amount of Nissl material. There is some slight change in the nuclei and a slight change in size. *B*, section from the upper thoracic region of the anterior horn, showing the same condition as in *A*. *C*, intermedial lateral column of cells showing normal structure. *D*, section of anterior horn region in the lumbar cord showing normal number of motor cells with no reaction. There is possibly a slight decrease in density. Cresyl echt violet stain; × 350.

meter of from 80 to 90 microns. Many showed considerable atrophy and were reduced to from 10 to 20 microns. None had reached the most advanced stage. (5) Right biceps brachii. This muscle showed considerably more change than those previously described. Most of the fibers were about 30 or 40 microns in diameter; the largest were 50 microns. Many showed nearly complete atrophy, measuring from 10 to 20 microns. (6) Right temporal. Most of the fibers showed nearly complete or complete atrophy. There were a few that showed only the early stages. The largest measured 50 microns; the smallest were 10 microns or less (fig. 4 *C*). (7) Left gastrocnemius. Nearly all the fibers showed practically complete atrophy and were too small to be measured accurately. A few partly atrophied fibers measured from 20 to 40 microns. (8) Right vastus medialis. This muscle showed the final stage of atrophy and probably complete disappearance of many fibers, as the number appeared greatly diminished. The atrophied fibers were too small to measure accurately (fig. 4 *D*).

Neuropathologic Study (Dr. H. H. Dixon).—Gross Examination: The brain, after preservation in 10 per cent of a neutral diluted solution of formaldehyde, U. S. P. (1:10) showed a normal topography. A close examination of the motor area of the cortex revealed a normal structure throughout. The meninges were normally attached and there were no adhesions. The cerebellum was of normal size and contour. There were no adhesions of the meninges around the cord and no change in size or contour. The roots were attached throughout, and no adhesions or evidences of change were present.

Microscopic Examination: Sections were taken from the motor area of the cortex, the region of the internal capsule, the basal ganglia and the brain stem at the level of the pons, and from the second and fourth cervical, the first and sixth thoracic, the first and fourth lumbar, and the first sacral segments of the cord. All the sections were embedded in celloidin.

The motor area of the cortex showed a normal number of cells, without reaction of any kind. The cell layers were of normal number and density. The myelin sheaths in this area and in the corona radiata were normal. There was no change in the number and density of the glial elements.

The internal capsule, globus pallidus, and brain stem at the level of the twelfth nerve appeared normal. The number and condition of the cells of the twelfth nerve were normal, except for some indication of shrinkage; the Nissl granules were of normal size and distribution.

The second (fig. 6 *A*) and fourth cervical, and the first (fig. 6 *B*) and sixth thoracic segments of the cord showed normal distribution and size of the anterior horn cells; the Nissl material was present, without evidence of reaction. The Weil stain showed normal fiber pathways. There was no evidence of adhesions of the meninges. The first and fourth lumbar segments showed that the cells in the anterior column were decreased in number by an estimated 30 per cent. There was much evidence of shrinkage, although the cells still appeared as functioning cells. There was Nissl material in more or less normal distribution. There was no reaction in the structure of the anterior horns. The vessels revealed no abnormality. There was no evidence of gliosis (fig. 6 *D*). The first sacral segment appeared normal throughout.

The peripheral nerves, with Weil and van Gieson stains, showed evidences of decrease and beading of myelin sheaths. The presence of fibroblasts inside the neurilemma was brought out by the cresyl violet stain. There was a distinct decrease in the number of large myelinated fibers. There was no evidence of change in the unmyelinated elements or of inflammatory reaction in the sheaths (fig. 7). Sections from the sacral plexus showed the same changes as those through

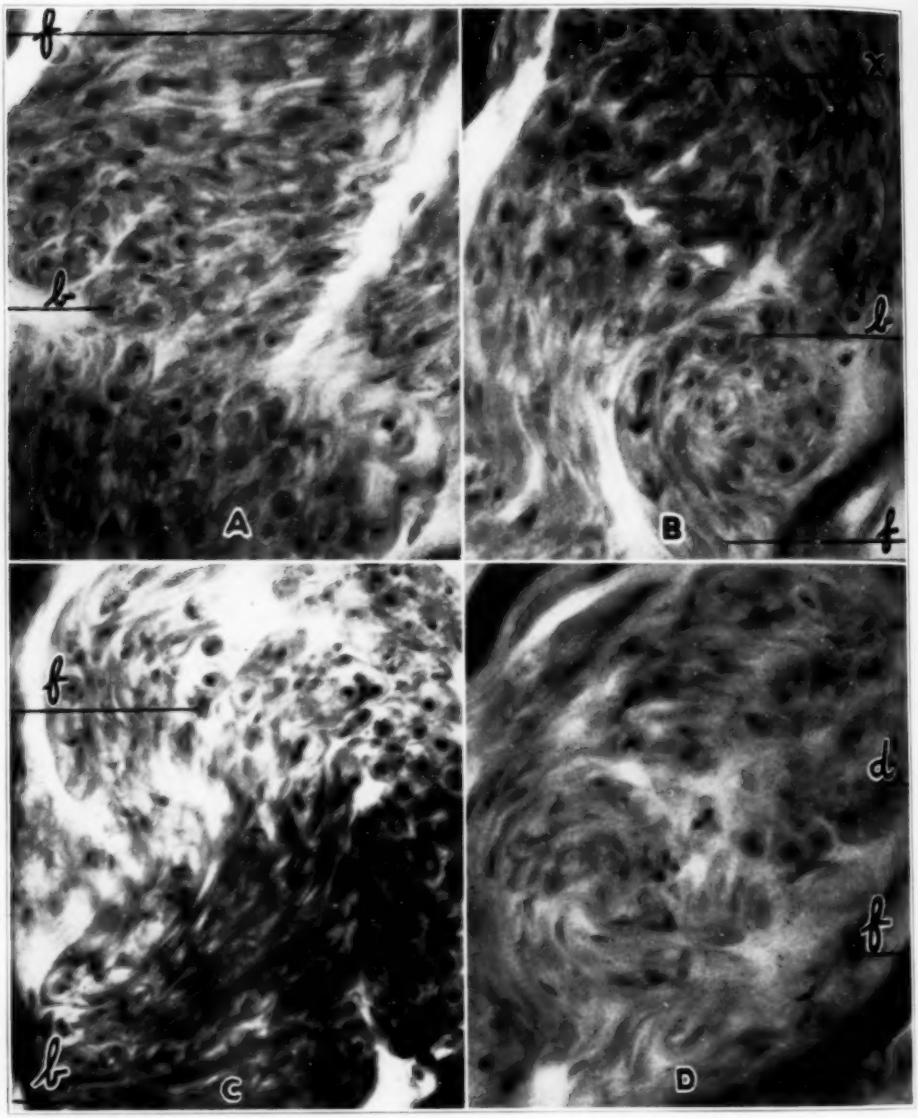

Fig. 7.—*A*, section of part of lumbar plexus showing slight beading of myelin and occasional invasion of fibroblastic nuclei. There are quite a few normal fibers. *B*, mixed nerve taken before division for muscular entrance, showing same condition as in *A*. *C*, a motor nerve showing marked increase in number of fibroblasts and decrease in number of fibers with beading and destruction of myelin. *D*, motor filament just before attaching to muscle, showing almost complete obliteration of fibers with marked invasion of fibroblasts. Fibroblasts are designated by *f*; beading of myelin sheath by *b*; normal sheath by *x*, and degenerated myelin by *d*. Weil stain, changed to show nuclei structure; × 350.

the twelfth nerve. The proximal branches of the musculospiral nerve in the biceps showed acute degeneration, with disappearance of a large number of fibers. A large number of fibroblasts were present in the sheaths; the unmyelinated fibers here were intact. The intrinsic nerves of the diaphragm and biceps showed gross degeneration. There were decrease and beading of myelin sheaths, fibroblasts inside the neurilemma and gross diminution in the large myelinated fibers. There was no evidence of change in the unmyelinated elements, or of inflammatory reaction in the sheaths.

COMMENT

The principal evidence of pathologic change was in the peripheral nerves; the changes in the lumbar sections of the card are interpreted as being a rather severe retrograde degeneration of the cells. This, we believe, is due to the condition of the peripheral nerves. In following through the nerve sections, the diminution of fibers increased as one approached the small muscle nerves, where a very large percentage of fibers were absent and were replaced by connective tissue. In the main trunks there was a decrease in fibers, but it was much less striking than in the smaller branches where the fibers were mostly motor.

Histopathologic study of the nervous system gave the impression that the degeneration is not due to an inflammatory process but has originated as a primary structural defect.

SUMMARY AND CONCLUSIONS

A case is presented of a symmetrical type of muscular atrophy, chronic and progressive in course, which had been under observation for over twenty years.

Three brothers were subjects of the same disease; one died without the condition having been studied pathologically; one forms the basis of this study; the third is still living at the time of this report, in an advanced stage of the disease.

The absence of group muscular involvement referable to the enlargements of the cord is noteworthy in all three cases.

The marked changes in the voluntary muscles reached a degree of almost complete disappearance of the fibers without evidence of inflammatory reaction.

The negligible involvement of the spinal gray matter and the apparently normal functioning condition of the polar cells is remarkable if not unique.

Noninflammatory degeneration of the myelinated elements of the peripheral nerves appears to constitute the primary pathologic lesion.

The suspicion expressed with reference to the possible primary structural defect is strengthened by the familial incidence.

325 Mack Building.

ABSTRACT OF DISCUSSION

Dr. William G. Spiller, Philadelphia: The omission of the word "spinal" in the title of this paper was evidently intentional, and the title chosen, "progressive muscular atrophy," becomes thereby somewhat ambiguous. Most muscular atrophies are likely to be progressive except the sharply limited forms from local causes. Preservation of the leading types is desirable, although some cases may be difficult to classify. In writing my chapter in Osler and McCrae's "Modern Medicine," I did not make separate types for subacute and chronic poliomyelitis, as these distinctions appear to me theoretical rather than practical. Amyotrophic lateral sclerosis may have a prognosis very different from that of progressive spinal muscular atrophy, and Dejerine showed, in 1895, in the report of two cases, that the latter disease existed for ten and eighteen years, respectively, without degeneration of the pyramidal tracts. It is well known that the duration of life in the former disease is usually limited to a few years. The separation of the two forms is therefore desirable.

In 1907, I published the report of a case, in which necropsy was performed, demonstrating the existence of progressive muscular dystrophy beginning in the periphery of the limbs and gradually spreading upward, and reference was made to the literature. The nerves examined were intact.

The case reported by Dr. Moleen seems to resemble especially the neural (Charcot-Marie-Tooth) type. The condition affected the male members of a family for two generations. The atrophy was general and was not confined to the periphery of the limbs, although it was more pronounced in these parts. Microscopically, marked atrophy of muscle fibers and decrease in the number of large myelinated fibers in the nerves were found. The nerve cells of the anterior horns of the first lumbar segment showed much shrinkage, and were regarded as diminished to about 30 per cent; this was considered secondary to changes in the nerves. The condition of the anterior horn cells between the fourth cervical and first thoracic segments is not stated.

The noninflammatory degeneration of the myelin sheaths of the nerve fibers is believed by Dr. Moleen to be the primary lesion and to have originated on a primary structural defect. It may be a little difficult to establish the correctness of this view. The shrinkage of the anterior horn cells is a common lesion in progressive spinal muscular atrophy. Bernhardt described a hereditary form of progressive spinal muscular atrophy in adults.

Dr. George A. Moleen: This case was quite puzzling to me.

The atrophy was more emphasized in the peripheral than in the proximal portions, in consonance with the finding of the more profound degenerative changes in the twigs of the nerves as they branched into the muscle distribution rather than in the proximal portions as they emerged from the spinal cord.

Dr. Spiller raised the question as to changes in the nerves, but it was not the opinion of Dr. Johnson or Dr. Dixon that such changes were present, chiefly because the characteristic changes in the nerve endings in the muscles were more marked than the changes in the muscles which had not become completely degenerated.

One is puzzled as to just how such a case should be classified. There are so many points of clinical interest that might be added here. Of particular interest is the fact that the muscles showed such pronounced objective changes in the patient during life.

The muscles, of course, presented no rigor mortis.

PRINCIPLES OF GESTALT IN COPIED FORM IN MENTALLY DEFECTIVE AND SCHIZOPHRENIC PERSONS *

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Wertheimer,[1] in investigations into the theory of Gestalt, used a series of figures, which he presented to a number of normal persons; he then had them describe what they perceived in order to discover what sort of visual "Gestalten" were formed and to determine what principles were back of optically perceived form. Some of the principles established by him were that optically perceived form, or "Gestalt," was determined by proximity of parts, similarity in forms, continuity of geometric forms and internal organization. These principles together formed the so-called "gute Gestalt."

It was thought that it would be of some interest to utilize Wertheimer's figures to determine if perception in schizophrenia followed the same principles. It was not possible to get patients with advanced schizophrenia to describe their perceptions, but it was found that many of even the most uncommunicative would copy the designs with pencil and paper. The same method was used with normal persons, as the problem is no longer one of visual perception but of visuomotor patterns. Neither will it always be possible to separate the two elements of perception and motility in the analysis of the results. Finally, fifty persons were tested, half with schizophrenia and half without, the latter half ranging in mental age from the lowest available to that of the superior adult. A relatively small series of Wertheimer's patterns were used. These were all copied from his paper,[1] except that the English "June" was substituted for his "Juni." Ten were chosen that seemed to cover the main principles involved. These are seen in chart 1.

According to Wertheimer, figure 1 should be so perceived that the dots would appear as a series of pairs determined by the shortest distance, in spite of the line starting with the greater distance or with a "remnant." Such a pairing would have been more readily perceived if the difference in the distances had been greater. This is an example of a "Gestalt" formed on the principle of proximity of parts. Figure 2,

* Submitted for publication, July 2, 1931.

* From the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital.

1. Wertheimer, M.: Psychol. Forsch. **4**:300, 1923.

according to Wertheimer, is perceived usually as a series of short slanting lines consisting of three units so arranged that the lines slant from right below to left above. It is also determined on the principle of proximity of parts. This is also true of figure 3. Figure 4 is ordinarily perceived as two units determined by the principle of continuity of geometric forms or internal organization. The three sides of a square are seen, with a bell-shaped form at the lower right corner. In the same

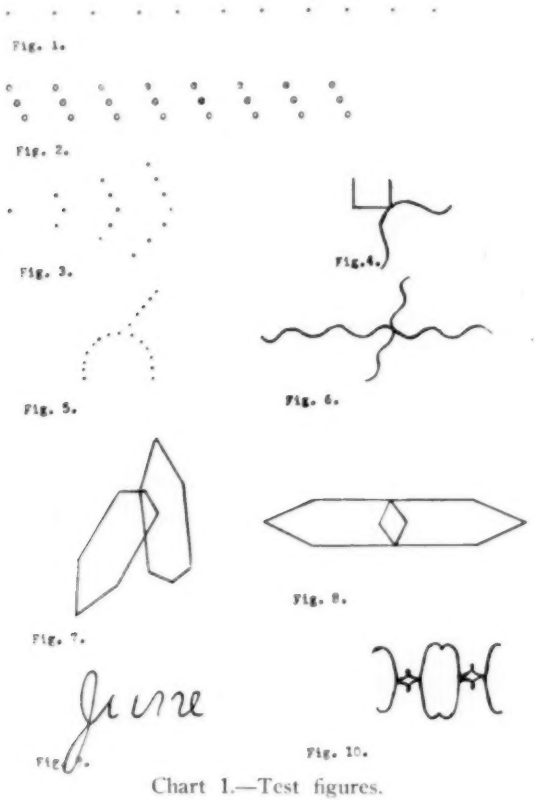

Chart 1.—Test figures.

way, figure 5 is seen as a part of a circle with an upright slanting stroke, made in dotted lines. Figure 6 is perceived as two sinusoidal lines with different wavelengths crossing each other at a slant. In figures 7 and 8 there are two figures made up of the same units, but they are rarely perceived as such, because in figure 8 the principle of the continuity of geometric forms prevails, which is here a straight line at the top and bottom of the figure. In figure 9 the separted parts are united to produce the "gute Gestalt" of the recognized form. In figure 10 the intended forms of W's and M's are rarely perceived. Again the

principle of continuity of geometric forms seems to prevail. Here it is the curved upright arm at each end and the more or less circular form in the middle. And so it is seen as a meaningless and rather elaborate design.

TECHNIC AND MATERIAL

The forms were each placed before the patient on a separate card, properly oriented, while being copied, so that there was no element of memory or recall. It was always possible for the patient to compare his final result with the original copy, and if there was any indication of dissatisfaction he was encouraged to try again.

The patients used in this experiment were all at the Springfield State Hospital, Sykesville, Md. The schizophrenic subjects had all been former patients at the Henry Phipps Psychiatric Clinic of Johns Hopkins Hospital, from which they had been sent to the Springfield State Hospital from two to fifteen years previously. The mentally defective subjects were all adult patients (over 25 years of age) at the State Hospital, and all had been without psychosis at any time as far as was known. The superior adults who were tested were physicians on the staff of the

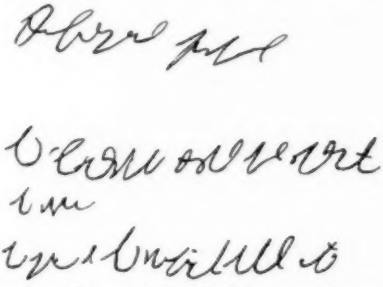

Chart 2.—Spontaneous writing of Bessie M., mental age from 1 to 2 years.

Phipps Clinic. The mental age of the mentally defective persons was determined at the time of testing by the revised Stanford-Binet scale. That of the schizophrenic subjects was not tested because of their failure to cooperate. In a few cases there were records of intellectual ratings previous to or early in the psychosis. Otherwise an effort was made to estimate the intelligence roughly from the school and industrial accomplishments. Intellectual rating of the superior adults was not deemed necessary. Only representative examples are here shown. They were all reproduced by direct tracing. Figures were rearranged to comform to the limitations of space, and some figures were omitted that did not seem of value. The fine dotted arrows and lines are mine, and are used to indicate the mode or direction of production when this is not clear from the figure itself and to emphasize the radial direction of parallel lines.

RESULTS

Mentally Defective Persons.—A subject with a mental age of between 1 and 2 years responded to her own name, walked and kept herself clean, but could not talk. She made forms on the paper of her own liking, which are of considerable interest, especially in the light of productions of the progressively higher mental levels. Her production is shown in chart 2. It does not resemble the copy, but is seen to resemble

closely handwriting in some unknown language. It had no evident meaning for this patient, but still it is made up of all the elements of written language and is broken into units closely resembling words. One might think that she had previously seen and learned to imitate handwriting, but when one observes that these simple minds cannot copy forms considerably simpler than this, and that they are not capable of any such memory feat, it is realized that this is not possible. It is of interest, however, that Arnent,[2] in studying the spontaneous and copied productions of small children, showed that children between the ages of 2 and 4 produce meaningless scribblings of a similar sort. The examples given by him [2] are considerably cruder than the productions in chart 2, owing, no doubt, to the better developed motor control of the adult who is mentally defective. Arnent claimed that the child's scribblings are probably an imitation or copy of adult writing, but inconsistently enough went on to show that in the next higher mental levels the children are unable to copy or imitate, but make forms without thought or resemblance to the copy in front of them and are unable to recognize or name their own productions. It may be, therefore, that at this low level the productions are the product of a motility response as, indeed, is claimed by Prinzhorn [3] who stated that in young children drawings are merely the expression of joy in rhythmic movement, and that the productions have no meaning for them. Also Gaupp [4] said that in children from 1 to 3 years old scratches and scribblings are only an expression of activity, and that meaning of form or ability to copy does not appear until 3 to 4 years of age.

A woman with a mental age of about 3 years was able to understand instructions and to endeavor to copy the forms that were presented to her. Her results are shown in chart 3. First is seen some of her spontaneous writing, which closely resembles that in the preceding case and also resembles most of her efforts at reproducing the forms shown to her. It may require careful analysis to make the assertion convincing that the productions in chart 3 are actual efforts to reproduce the figures seen in chart 1. Most of them are composed of small looped units perseverated in a horizontal line, each one varying slightly in form from the previous one, in such a way that there is a gradual departure from the simple looped form for a while, and then the variation reverses itself and returns to the simple form again. Figures 1, 2 and 3 are made up

2. Arnent, W.: The Mind of the Child, London, Kegan Paul, Trench, Trubner & Co., Ltd., 1926.

3. Prinzhorn, Hans: Bildnerei der Geisteskranken, Berlin, Julius Springer, 1922.

4. Gaupp, R.: Psychologie des Kindes, Leipzig, B. G. Teubner, 1928.

in this way of a perseveration of the horizontal plane in the vertical direction without regard to Gestalt. In figure 1 there is no tendency to pairing. The dots become loops and even the horizontal plane is perseverated. Figure 2 is similar. In this patient the tendency to perseverate did not carry beyond the third line. Others of a similar age level would perseverate in both directions until they had covered the paper. Even figure 3 is reproduced in the same way without regard to the Gestalt principle involved in it. There are three horizontal lines of

Chart 3.—Maggie M., mental age from 2 to 3 years.

loops, with the middle one a little longer than the others. Figure 4 may not seem to resemble the form offered. The reproduction is much smaller, more nearly conforming with the units of the other figures, but departs from the other reproductions enough so that the middle part of it somewhat resembles the form given. Still, it is not reproduced according to the Gestalt principles, because, although the three-sided figure is fairly complete and there is finally a form at the lower right hand corner, these two parts were not made separately in the way that will be shown in the higher mental levels, then there are perseverations

of loops on either side. Figure 5 seems to resemble even less closely the test form, but there is some apparent effort to enlarge the curved forms and to make an upward stroke, although again not in a separate way that would indicate the Gestalt organization of the figure. Figure 6 shows clearly the effort to make a continuous sinusoidal line, with at least three efforts at crossing. But there is also a fragmentation of the figure. This may be a tendency carried over from the former figures which were made of the looped units. This tendency to carry over a part or a whole of a former drawing into the next object offered is a tendency recognized in children (Arnent [2]). But fragmentation of perceived form has also been recognized as a common tendency in optic imagery by Kanner and Schilder,[5] and in sensory perception by Schilder and Bromberg.[6] In figure 7 can be seen a crude effort to make two upright rectangular forms that are separated from each other, are parallel, are not slanted and do not cross. These difficulties in crossing and slanting will be discussed again where it is more clearly illustrated. In figures 7 and 8 are seen the only evidences of Gestalt produced by this patient, and here, indeed, they are actually exaggerated. Thus, already one may begin to believe that there are different kinds of Gestalten that are perceived or reproduced at different mental levels. Figures 9 and 10 (not shown) were made by the patient by a perseveration of the looped form such as in figures 1 to 6, but with no apparent resemblance to the test forms.

A reconsideration of chart 3 will now show that the horizontal lines are never straight, but in themselves show a rotational or vertical direction. In subsequent cases it will also be seen that they are never parallel, but always radiate toward or away from each other so that the directional movement as expressed by perseveration is radial. Thus, vertical, directional, radial and wave movement in some way seems to be the basis of the primitively reproduced visuomotor pattern.

From this, one may obtain the following corollaries: fixed points are not reproduced as such, but as looped forms, and a straight line is not reproduced as a function of two fixed points, but as a function of a radial directional wave movement. Therefore, parallel lines, angulated forms and crossed forms present great difficulties.

Many similar phenomena have been found in young children. Baldwin [7] followed the course of his child in her ability to draw and copy from the nineteenth to the twenty-seventh month. At the earliest age there was "the simplest and vaguest and most general imitation of the

5. Kanner, Leo, and Schilder, Paul: Nervenarzt. **7**:406, 1930.

6. Schilder, Paul, and Bromberg, Walter: J. Nerv. & Ment. Dis. **72**:489, 1930.

7. Baldwin, J. W.: Mental Development, New York, The Macmillan Company, 1903.

teacher's movements, not the tracing of the mental picture. There was no semblance of conformity between the child's drawing and the copy. She could not identify it herself." He found that at the earliest age (19 months) there were only sweeping whole arm movements from the shoulder. A few months later, she began to flex the elbow and wrist, and at 27 months she was able to manipulate the fingers. At that time her productions were made of loops in the clockwise direction, with an emphasis on the horizontal plane. It was also brought out that in each new drawing there was a tendency to carry over a whole or a part of the previous drawing. In this one sees how important in the young child are the motor elements, and in fact it appears that the motor and perceptive elements are dissociated. Similar points were made by Prinzhorn,[3] already quoted, and by Arnent,[2] who found that at 3 years there was no thought of resemblance between the child's drawing and the model, but that the child seemed to draw from memory (sic?) and not from nature even when the object was before it.

In the Merrill-Palmer intelligence test for preschool children, copying a circle is the accomplishment of a 3 year old child, copying a cross that of a 4 year old and copying a star that of a 5 year old; in the Stanford-Binet test it is determined that a normal 4 year old child can copy a square, whereas a 7 year old child can copy a diamond.

Movement, fragmentation and curving of forms were shown in the normal optic imagery by Kanner and Schilder,[5] and also difficulties with crossed and angle forms in cutaneous sensory imagery by Schilder and Bromberg.[6] Also Stein and von Weizäcker[8] and Stein[9] showed that in the pathologic disintegration of sensory phenomena it often happened that a circle or an arc was perceived instead of a cross. Stengel[10] showed in similar types of disturbances that in general there was a tendency to experience a sort of a crooked or bent line instead of a straight one. Von Weizäcker also found in optic disturbances that crossed lines or lines forming acute angles were perceived as parallel lines.

A person with a mental age of 3 years (chart 4) shows many of the same principles but some additional accomplishments. Figure 1 is a series of small loops (no pairing) with a tendency to vary the loop formation in such a way as to emphasize the horizontal base. The subject perseverated indefinitely in the dextrad direction, but did not perseverate the horizontal plane. Figure 2 is still produced in horizontal lines, and there is some suggestion of vertical planes, but no slanting; thus there is no regard for Gestalten in either of these. Figure 3 was recognized

8. Stein, H., and von Weizäcker, V.: Ergebn. d. Physiol. **28**:657, 1928.
9. Stein, H.: 37 Kongr. f. inn. Med., Wiesbaden, 1925.
10. Stengel: Deutsche Ztschr. f. Nervenh. **99**:31, 1927.

as a problem different from the previous ones, but it proved to be an unsurmountable task. The subject attempted the horizontal and vertical perseverations. However, her second effort may be considered a real representation of the Gestalt principles involved. The tendency to reproduce a series of dots in a line has also been seen by Stengel [10] in thalamus disturbances, and by Stein and von Weizäcker [8] in mescaline poisoning. Figure 4 was tried four times. It is of interest that the first effort is small and does not deviate much from the unit used, for example, in figure 1, and may have been carried over from

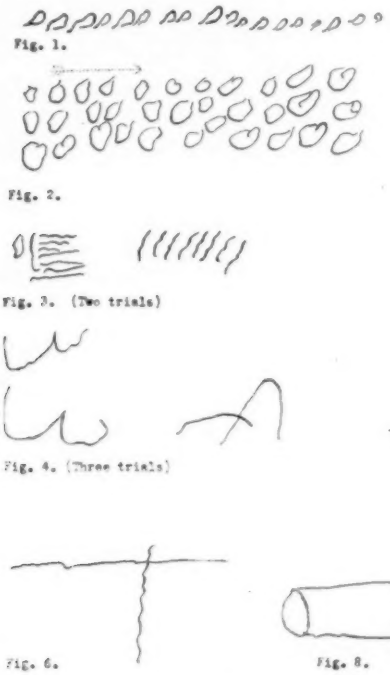

Chart 4.—Ella R., mental age 3 plus years.

the previous figures. However, each effort departs more from this small size. It is also of interest that what is apparently here interpreted as crossed lines was not accomplished without considerable effort. There is some suggestion here that this figure is seen in two units, or Gestalten, but it is not complete. A simple crossed form is accomplished in figure 6 with a definite suggestion of sinusoidal formation, but it is a right angle and not a slanting crossing. Figure 8 is crude, but the principles of Gestalt are well illustrated. I do not know if it is significant from the consideration of directional determinants that at both this and the previous level, the left end of this figure is closed.

Chart 5 was produced by a woman with a mental rating of 5 years. She could talk and help with simple work about the ward, such as scrubbing. She could not write her name or any other meaningful sign. Her spontaneous production is seen at the top. It was produced in the sinistrad direction. This tendency is known to be common among children of this age as well as among mentally defective persons (Orton,[11] Gordon[12]). In figure 1 there is a tendency for the loops to become dots, but still the loops predominate. In figure 4 the Gestalt

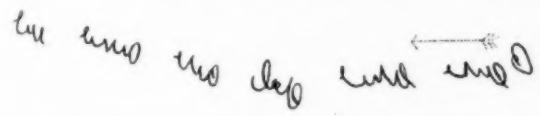

Fig. A. Spontaneous writing. (Written in sinistrad direction)

Fig. 1.

Fig. 4.

Fig. 5.

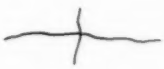

Fig. 6.

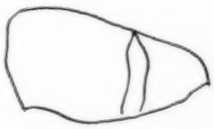

Fig. 8.

Chart 5.—Elizabeth C., mental age 5 years.

principle is apparently not only in evidence but exaggerated. The figure itself was perseverated (there were several more), and the tendency to make the Gestalt units so small may be an example of micropsia or simply a reproduction by reiteration of the small units such as the subject used in figure 1. The separation of the two Gestalt units is a tendency that occurs frequently in subsequent cases. It may itself be

11. Orton: "Word-Blindness" in School Children, Arch. Neurol. & Psychiat. **14**:581 (Nov.) 1925.

12. Gordon: Brain **43**:4, 1920.

an indication of movement in sensorimotor phenomena. Figures 5, 6 and 7 are crude efforts, but in all the Gestalt principles have been active, though the more elaborated function of the exact relationships of the parts to the whole is neglected.

Chart 6 was produced by a patient with a mental age of 7 years. She was able to write her own name, but could not read and did not recognize "June." In figure 1 again there is some slight tendency for

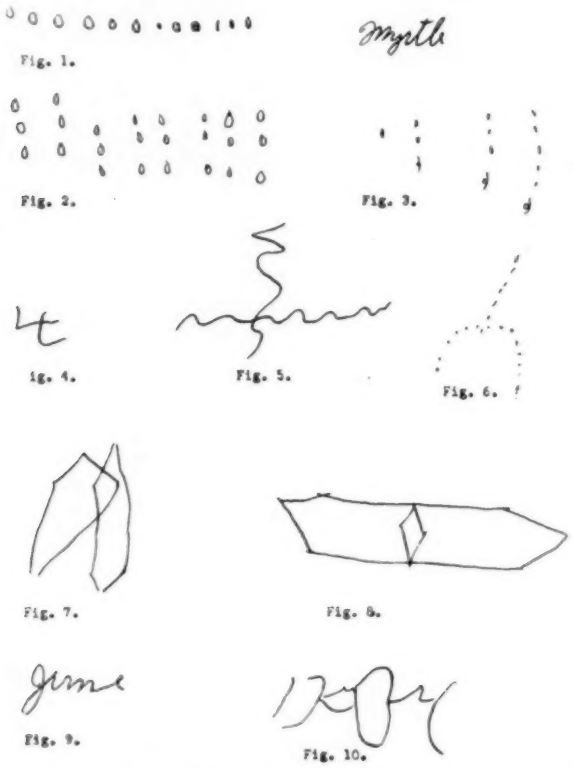

Chart 6.—Myrtle Mc., mental age 7 years.

dots to become loops. For the first time figure 2 is produced as a series of vertical lines or in accordance with the Gestalt principle, but there is no slanting. Also figure 3 is produced in vertical planes or Gestalten, and there is a definite effort at dot formation, but only the slightest suggestion of angle formation. Figure 4 is again small and reverts to the simpler type, away from the principle of Gestalt. Figure 5 is well done, except that the crossing is not slanted. Although radial tendencies would seem to be an adequate basis for slanting, consciously applied slanting forms seem to present difficulties that only the more intelligent are capable of accomplishing. Figures 6, 7 and 8 follow the principles of

Gestalt. Figure 9 was recognized as a written word but not a meaningful one. Figure 10 is incomplete. Thus, it is seen that at a mental age of about 7 years, many Gestalt principles are established, and form begins to take on meaning.

At the 10 year level, pairing in figure 1 and slanting are still difficult (chart 7). Here the deviations (in fig. 2) may be considered to be due to radial and vertical tendencies, or at least to tendencies toward movement of some sort. Two other points of interest come out in chart 7. In figure 5 is seen an extreme example of what is

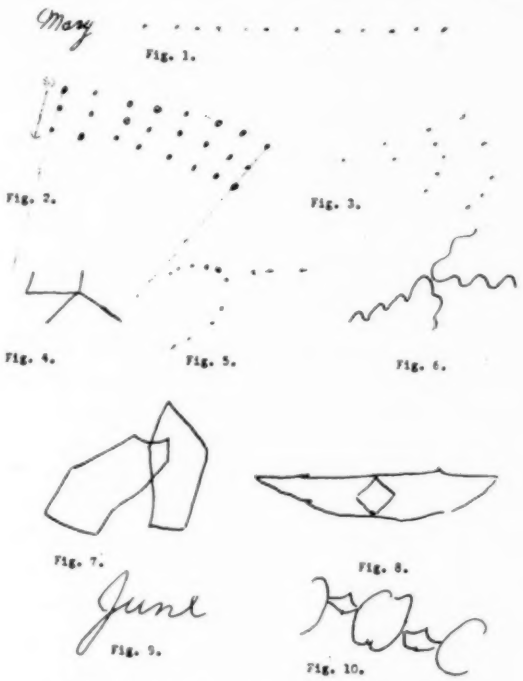

Chart 7.—Mary H., mental age 10 years.

observed persistently at all mental levels to some extent. It is a tendency for the whole figure to rotate in a clockwise direction. It may be due in part to the upright stroke that slants in a clockwise direction and exaggerates an inherent tendency to rotational movement. Also, in this instance figure 6 was not perceived and reproduced as crossing sinusoidal lines, but as two rounded angular forms that approximated each other. This is not a peculiarity of this age, but occurs in a minority of cases at various ages. It is also seen in chart 8 by a superior adult. It may be an expression of the difficulty in crossing lines, whereas the angular formation permits of a curving line and not a fixed point angle.

Superior Adults.—Only in the tracings of superior adults (chart 8, compiled from several subjects) does one observe the grouping into pairs in figure 1 (this principle was not always recognized and reproduced by this group) and the slanting line formation in figure 2. In no instance was figure 8 perceived as made up of the same units as figure 7. Even in figure 7, it was rarely perceived that the two parts were similar. Each unit seemed to have some influence on the other.

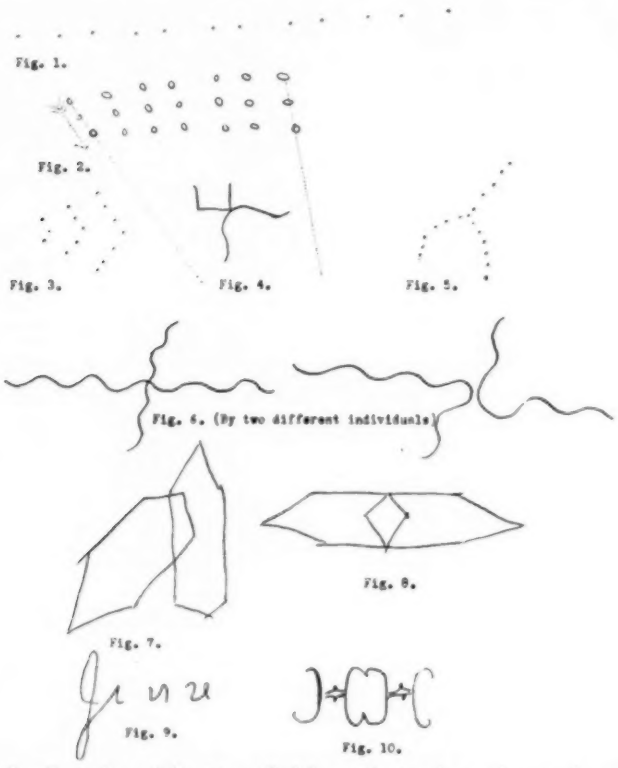

Chart 8.—Superior adults (compiled from the tracings of several persons).

The tendency for the base line in figure 8 to become flattened out is also of interest. It is an expression of emphasis of the horizontal base line, such as was vividly seen in figure 1 of chart 4. The joining of letters in written language at the lower level rather than at the top is probably an expression of the same thing. In no instance was figure 10 perceived as composed of W's and M's except by one superior adult whose initials happened to be W. M.: he said he had once used a monogram of this type, but thought that the resemblance of the form to his initials was just a coincidence and that it was not intended that way, and so he did not reproduce it in that way. It was evident

that all persons above the mental age of 7 (who were able to read) saw in figure 8 nothing but the intended "June." Another difference in the different mental levels was shown in connection with dotted lines, such as is seen in figure 1 and figure 5. At the lowest levels, these dotted lines only accentuated the tendency to perseverate the usual loop-formed unit. This was continued in both directions without consideration for the limitations of the sample form, until stopped by the examiner or the limits of the paper. At about the mental level of 7 or 8 years, this perseveration was controlled, and then the number of the dots and the form they took became important. The exact number of the dots was counted and reproduced even in figure 5, and more surprisingly in a more elaborate and meaningless form which was used for awhile, making the test very laborious. In the superior adults, as soon as the principle of the form was recognized the number of the dots became unimportant. They were rarely counted in figure 5, and in figure 1 if the principle of pairing was recognized they were not counted, but enough dots were reproduced to show the principle; if the pairing was not recognized, the dots were counted and the exact number reproduced. In figure 2 the tendency for the angle of the slant to vary enough to give a radial form to the lines is brought out. There are other tendencies in this figure suggesting flattening and spreading, probably in connection with the general tendency to motion in sensorimotor phenomena. One may conclude from these experiments that the principles of Gestalt are of different types, some occurring at only the more highly integrated intellectual levels, while some appear at the most primitive levels and then seem to be actually exaggerated by such tendencies as spatial separation or perseveration of individual units.

Schizophrenia.—It was of considerable interest that many schizophrenic patients who had apparently been out of contact and uncommunicative for years and who did not speak or make any spontaneous productions by writing were still willing to copy these impersonal forms. Probably 7 or 8 years was the lowest mental level, so that there is nothing to compare with the more primitive mental stages. Perhaps none reached as high a mental level as the superior adults tested, though some were certainly of superior intellectual level.

Elizabeth C. (chart 9) went to school only a few months before her mother died, and she had to stay home to look after her younger siblings. At 15, she went to work in the mills. At 22, she married and had three children. At 40, she became disturbed and worried about finances, thinking she heard noises at night. At the Phipps Institute, she was preoccupied with religious ideas, draping herself like a nun, and fearful that she would have an operation performed on her. After fifteen years at Springfield State Hospital, she talked of "punishment from God," of being

"milled in the mills," etc. She was manneristic in speech, expression and gesture, and showed marked vasomotor disturbances. She had vivid hallucinations in the visual, auditory, olfactory and somatic fields, with some elaboration into persecutory delusions.

Her productions show (chart 9) many of the characteristics of the 7 year level. There is an indefinite perseveration in the horizontal direction in figure 1. Figure 2 is produced in the vertical planes, but slanting is absent. Figure 3 is of special interest. It, too, was produced in vertical planes; thus the left-hand dot is correctly placed, the

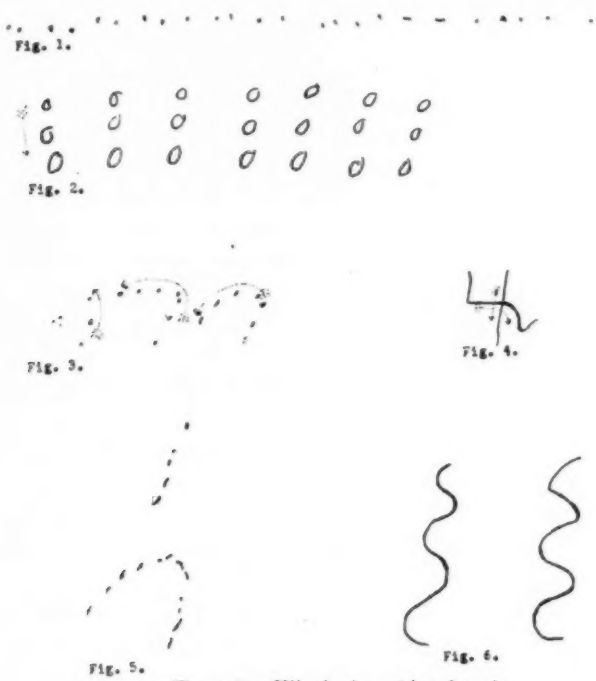

Chart 9.—Elizabeth, schizophrenic.

next three dots are properly related to it and there is a suggestion of angulation in this series; but the next series is an angulated form consisting of seven dots that have been rotated in the counter-clockwise direction, and the next series of seven dots have been rotated in the same way, but even further. Here there has been a dissociation by a rotatory disorientation of parts determined by the principle of Gestalt. Figure 4 was produced contrary to the Gestalt principles by a continuity of the horizontal line, which was crossed by a continuing vertical line. In figure 5 there is a dissociation of parts both spatially and by a rotatory disorientation of the circular part in relation to the upright stroke, although it seems probable that it is the very connection

of these two parts that causes this figure to tend to rotate. Figure 6 is a most interesting example of dissociation both spatially and by a rotation at an angle of 45 degrees. This compares with the observations of Stein and von Weizäcker [8] in centrally determined disturbances in vision where crossed lines or angles were persistently seen as parallel lines.

Rose M. (chart 10) came of a family in which many were mentally defective, and two others were also in hospitals with associated psychoses. She could not get

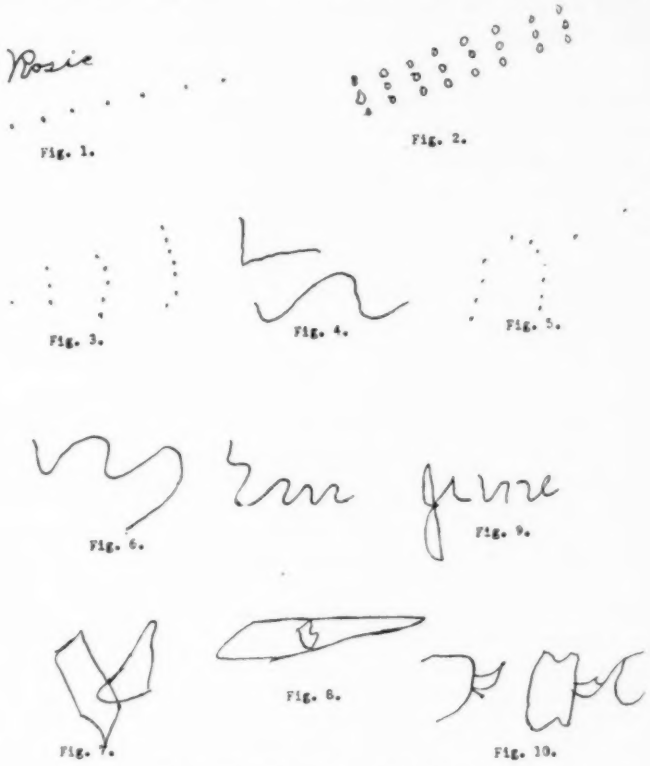

Chart 10.—Rose M., schizophrenic.

beyond the fifth grade, and then began to chase after boys in such a foolish fashion that they made her the butt of many pranks. Her father beat her in an effort to keep her at home, and she passed into an acute state of fear in which she was afraid she was going to be killed, heard voices to that effect and looked up to see visions of Heaven. At the Phipps Institute, at the age of 17, she passed into a catatonic stupor and was transferred to the Springfield State Hospital, where for eight years she had remained mute, drooling saliva, resistive, untidy and fearful of any change in her routine. The pupils were inactive to light, and there were vasomotor changes in the extremities. She was totally uncommunicative, except in the writing of her name and in the copying of these test forms.

Her productions (chart 10) show the general characteristics of a 7 or 8 year level. Several other things are also seen. In figure 3, the difficulty in angulation is shown, and also the tendency to reduce the whole figure to the horizontal plane which again is an exaggeration of a tendency found in the lower mental levels. In figure 4 there is a separation of the parts of the picture, and one part is incomplete. In figure 6 there is again the separation of the two parts and evidence of the difficulty in crossing lines. Here, however, the result is best understood by a comparison with the drawings of the normal persons who reproduced this figure not as two crossing sinusoidal lines but as two approximating sinusoidal rounded angles (charts 7 and 8). There is also simply a spatial separation of the parts in a horizontal and vertical direction. Of course, the productions in charts 7 and 8 may be looked on as the result of normally occurring difficulty in crossing lines, which is here accentuated. Separation and incompleteness of parts is also seen in figure 10 (compare with fig. 10, chart 6). Thus one observes a breaking down or dissociation in the principles normally underlying optic-motoric patterns, but in no regular way, for it is not a simple set-back to a lower mental level; different principles are dissociated in different parts.

Alma B. (chart 11) was an orphan. She reached the eighth grade and then became a nursemaid in a family, where she cared for six growing children until she was 35, when she was no longer needed and was relegated to the attic to sew. She became depressed and seclusive, and had the idea that men on the street were watching her. She went into a religious ecstasy, and said she had the power of healing and the power of conception. In the Phipps Institute she explained that she had been lonely and wanting love until she found it in Jesus, and after that everything was changed and she was happy. At the Springfield State Hospital, she said that she was the second Virgin. That was fifteen years ago. After that she had had two remissions during which she got along fairly well in the outside world, until she went into a catatonic stupor in which she was mute, soiling, tube-fed, resistive and irritable. In the course of several years she passed from this into a hebephrenic state, associated with a marked tic of the lips, in which she ejected saliva in an explosive tonic click whenever she initiated speech. She identified other patients as the children that were formerly her charges. Her speech showed marked dissociated schizoid features, and there was an incoordination of the muscles of the face, hands and of the gait.

In her productions (chart 11) there are many interesting features. Her inability to write her own name, owing to fragmentation and perseveration of parts, is shown. In general, her productions show the characteristics of a mental level of from 7 to 8 years. Dots are interpreted as loops, and yet the function of slanting appears. Many disorientations appear. Figure 1 was produced in a vertical plane though the figure lying before her was in the horizontal plane, so that at the completion of the task the two forms lay before her at right

angles to each other. As will be seen later, this occurred frequently. In figure 2, the slanting of the first vertical plane initiated a slanting of the whole figure. This was seen also in the nonschizophrenic persons of lower mental levels and probably is in line with the tendency to counter-clockwise movement which is accentuated by the slanting form. Figure 3 requires careful analysis, but the principles involved are simple and the same as have been seen before. Dots are given as the primitive loop. Beginning at the left there is first the single loop

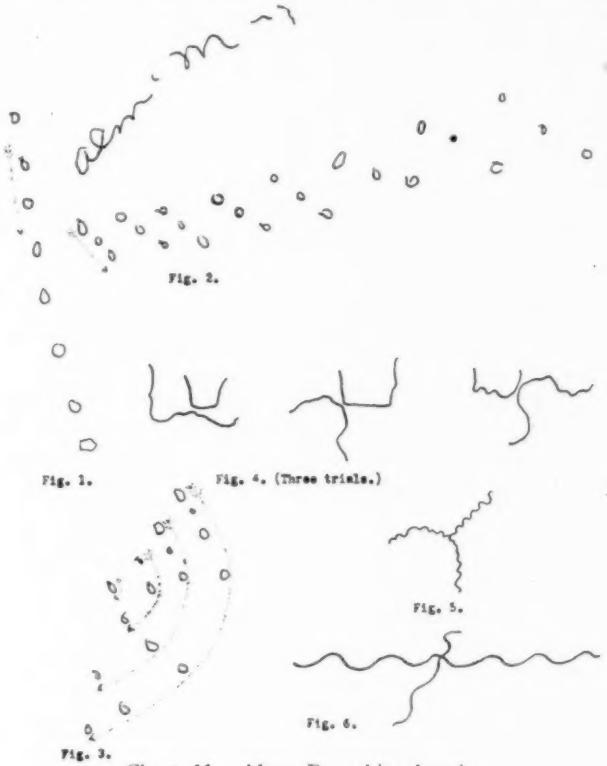

Chart 11.—Alma B., schizophrenic.

and then in proper relation to it three more with a suggestion of angulation. So far it is correct, and thus it compares with figure 3, chart 9. In the next plane, the upper three are properly placed, but the lower two are separated from the upper by a considerable distance, and in the last plane, though the upper four are properly placed, the lower three are again separated to the same degree as in the previous series. Thus, the left and upper part of the figure is correct, but the right lower part is dissociated by a clockwise movement; but the separation is not in accordance with the Gestalt principles in this

case, as it was in the same figure of chart 9. What determines the parts disturbed is not apparent. The patient made three efforts at figure 4 and finally succeeded in the third effort. The second is wrong only in that the lower bell-shaped figure is approximated to the lower left corner of the upper figure rather than to the lower right corner, but in the first effort, besides this, the lower figure is also turned upside down. Here the individual parts are determined in accordance with the principles of Gestalt, and the difficulty in associating them is a disturbance of a higher integrating function. It seems characteristic of

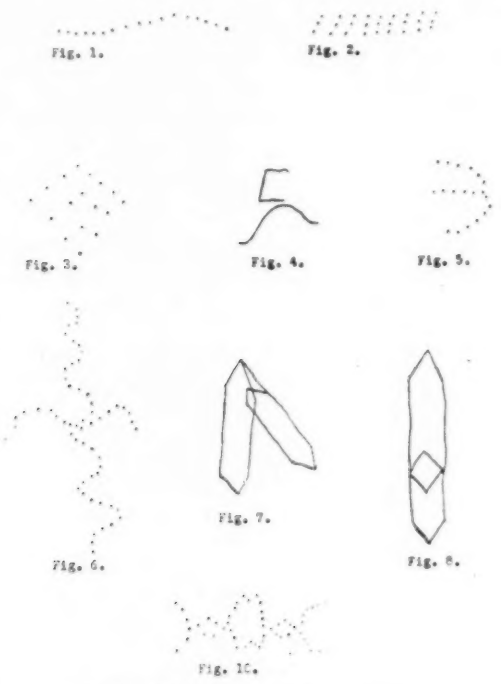

Chart 12.—Edna S., schizophrenic.

the schizophrenic subjects that one part of the figure is disoriented in relation to another part, or that the dissociation of parts is so marked that one part does not help in the orientation of another. To see the patients actually struggle with these simple forms is very impressive. They are obviously painfully disturbed by their difficulty in accomplishing what seems such a simple task. Even at the end they often seem in doubt as to whether they have finished the task satisfactorily.

Edna S. (chart 12) came of a family in which many on both sides were psychotic and mentally defective. Three others beside the patient had been in the Springfield State Hospital. After the death of the father, she and the mother went

to live with a widowed maternal cousin when she was 14. She never helped with the housework, never had any friends or associates, and never held a position for more than a few weeks at a time. At 29, she began to talk about being engaged to her widowed cousin and implied that there had been illicit relations. This was all denied by the cousin. She said that she was being talked about, suddenly became excited and said that she had become color-blind, that every one was rushing about and crowding around her and acted as though they had bad news to tell her. At the Phipps Institute she was confused, suspicious and resistive. She felt that some one had put a spell on her and spoke of being persecuted by Catholics, Germans and her family, and she talked of religion and war. Examination after ten years showed that she was apathetic, soiling, needing constant nursing care, manneristic, blocked and fragmentary in speech, and using numerous neologisms. There were tremors and incoordinations of the fine muscles of the hands and face, and the pupils were inactive to light.

Her reproductions (chart 12) show some interesing points not brought out in any of the previous ones. There is a marked tendency to micropsia, seen especially in figures 1 and 2. There is a tendency to perseverate from one test form to the other, especially in regard to the use of dots, as seen in figures 2, 6 and 10. There is a tendency to change the horizontal plane to the vertical, as has been seen before, in figures 3, 6 and 8. Owing to rotation, which is a more primitive tendency than horizontal planes, there is a tendency to dissociate parts of a figure by disorientation, seen in figure 4 and especially in figure 5, where the half circle is rotated in the clockwise direction, and the upright stroke is actually placed inside. Here again one sees that, though the tendency to rotate this figure is apparently accentuated by the position of the upright stroke, still this member itself is dissociated from the figure, and the rotational movement of the whole figure is very strong; thus the dissociation is obviously functional and not complete. It may be said therefore that the rotational form is characteristic of schizophrenic dissociation, and that it is never an immutable tendency and never total or regular in its functioning.

The rest of the patients were persons whose original intellectual endowment was average or higher. It might be assumed that the higher the intellectual level, the greater the number of possible dissociations as the integrative and associative functions are more elaborate.

Bern. C. (chart 13) graduated from high school with honors and did outstanding work in a music conservatory, where she both studied and taught. She became involved in two or three homosexual attachments, between the ages of 18 and 28, with music teachers. One of these with whom she was then living, died when she was 28, and she became very depressed and unproductive in her music. Her fear of failure aroused a good deal of agitation, indecision and mulling over of old complexes. At the Phipps Institute she showed first a period of hypomanic behavior, followed by depression with suicidal efforts and then a stupor from which she evolved with delusions about lines of force that connected everything

and made circles all about her, which actually terrified her. At the Springfield State Hospital, she went through many phases, in some of which she made feverish but poorly directed efforts at piano practice, planned elaborately to rehabilitate Russia and France (after the World War), or planned to go to New York and live the Bohemian life of a musician. Her former aversion to her father, because he was "coarse and sexual," and dependence on her mother changed to a denial of the identity of her mother, to mistreating her whenever she was around, to identifying as mother her several homosexual lovers, and to demanding attention of her father. When this paper was written she was quite dilapidated, obese and sluggish,

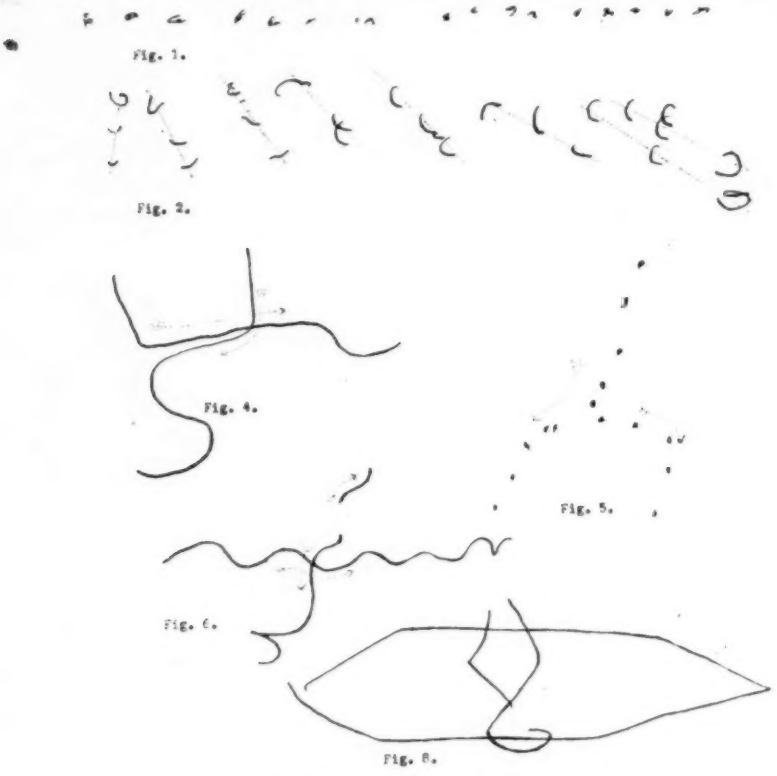

Chart 13.—Bern. C., schizophrenic.

talking constantly at random so that her speech was difficult to follow. She soiled herself and needed nursing care.

Her productions (chart 13) show pairing in figure 1 and slanting in figure 2, though carelessly done. Figure 4 was made contrary to the rules of Gestalt (see also chart 9), neither in accordance with the principles of proximity of parts nor of continuity of geometric form or internal organization. It starts in the upper left corner, but continues the horizontal base of the square form into the bell-shaped form, and then a cross piece is added. It appears that the perception of horizontal

planes is particularly strong at a rather primitive level, and it here has precedence over geometric forms. In figure 5, also, the rule of Gestalt is broken, and the figure is started at the top and passed down directly to the left side without much regard to the circular form. In figure 6, the horizontal line was produced and the cross piece added to it in two parts. Perhaps this is an expression of a tendency to avoid crossing lines, though in figure 4 crossed lines are preferred to the more

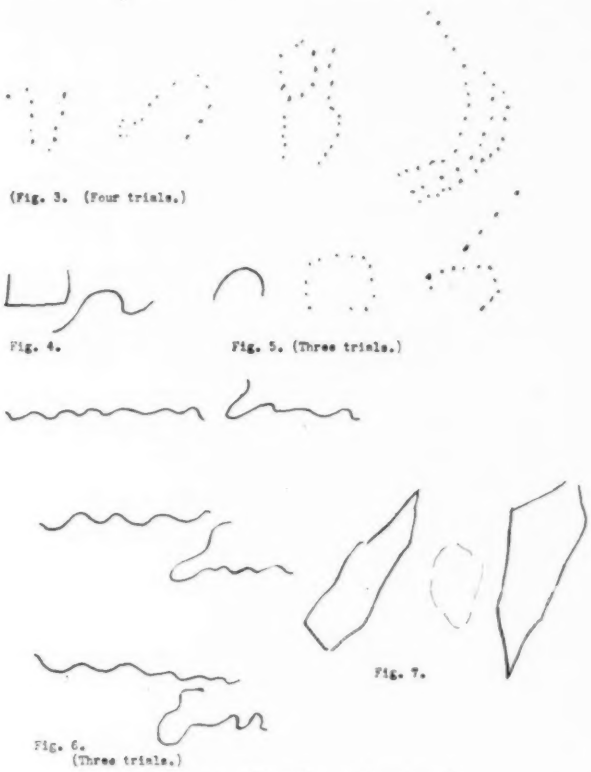

Chart 14.—Mae L., schizophrenic.

integrated way of recognition of geometric forms, but apparently the positive tendency to produce horizontal planes is the strongest tendency. Figure 10 is also similar in both.

Mae L's (chart 14) father, of whom she was very fond, committed suicide when she was 15. She had "nervous prostration" after this for several weeks. She quit high school in the second year and took up stenography. But in her work she was overconscientious and sensitive, and became increasingly worried about her inadequacy and tendency to preoccupations. She felt that her fellow employees were talking about her. She quit two positions at 21 because she felt inadequate. She became sleepless and self-reproachful and spoke of her family being disgraced

and killed by her masturbation. She became blocked in speech, saying German spies were listening to her. At the Phipps Institute she became stuporous, nearly mute and incontinent; she was tube-fed and resistive, demanding release because "I ought not to be here." For six years (to the time of writing) her behavior has been the same, except for an increasing apathy and diminishing interest. Her only spontaneous productions were "Too late" and "Father" and "I ought not to be here."

In copying the test forms (chart 14) she showed some obvious difficulties. She tried them over several times and seemed definitely puzzled. Thus in her four efforts at figure 3, which are not altogether intelligible, the principles of Gestalt seem to be in the foreground. In figure 4 there is a dissociation by spatial separation and a slight disorientation of the lower part. Her three efforts at figure 5 show in the first a tendency to carry over from the former figure both as to size and form, and in the use of a continuous line inclosed at the bottom (horizontal plane) instead of the upright stroke being applied. The third effort is satisfactory, though there is still some effort to close the figure at the bottom. Figure 6 is of interest. In her first effort she accomplished two lines lying end to end, one having a little upright stroke. Thus there is a dissociation by directional distance and rotation, and also the horizontal plane is accentuated and the lines are not crossed. In the second effort she brought the lines closer together, tending to make them parallel and accentuating the upright stroke. The third effort carried this a little further, but she never got them together or got them crossed. In figure 7 there is also a wide separation of the two parts with some apparent confusion about the space between them. One almost seems justified in assuming that the little formless figure between them is some effort to account for a space that she is in doubt about.

Chart 15 is the production of a patient in an interesting case of spontaneous remission or recovery from schizophrenia.

Pearl T's mother went to a state hospital with dementia praecox when Pearl was a small child and had been there for thirty years, now being in a "deteriorated vegetative" condition. Pearl was cared for by a step-grandmother. She was a model child, submissive, affectionate and sensitive. At puberty, she fancied sex relations and pregnancies. She said later that she and her only younger brother had had sex relations at this time, and that she was aware of gossip about the probable relations between her father and her step-grandmother, and that she had heard for the first time that her mother was in a state hospital. She showed a change in personality in which she became hostile to the step-grandmother. Her work as a music teacher failed her, and she did nothing about the house but make trouble. She thought she was persecuted by her family and by the neighbors, and heard voices to this effect. She became violent and dangerously assaultive to the step-grandmother. At the Phipps Institute a diagnosis of schizophrenia was made, and the mental age was found to be 9 plus years. At the Springfield State Hospital, she gradually became worse and spent ten years in the cottage for the most

disturbed patients, where she was out of contact, talking in a word salad, beating and pounding and screaming, and was described as "deteriorated." She was never visited by any of the family and had no contact with the outside world. Two years ago, she made a spontaneous recovery while in the cottage without known stimulus. At the time of writing she is a likable and industrious person, but without insight into her past experiences and unable to account for the passage of the years. By similar mental tests to those that she took fifteen years ago, she now rates a mental level of 11 years and 9 months, or a gain of nearly three years.

In chart 15 it will be seen that the reproductions are in keeping with the mental age, and there is no schizophrenic dissociation. There is no

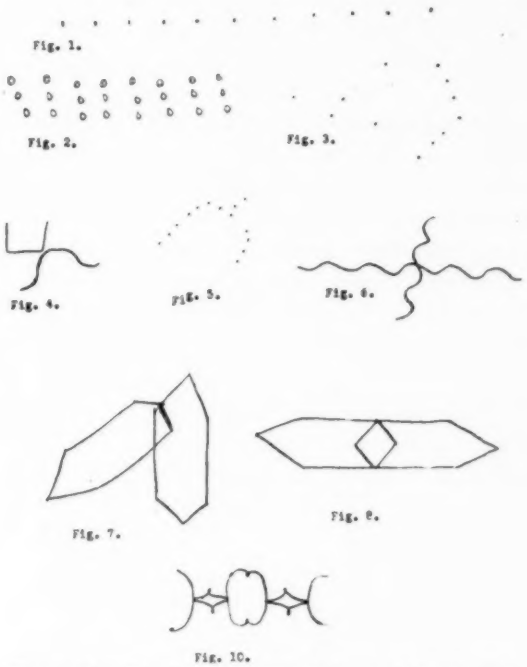

Chart 15.—Pearl T., recovered from schizophrenia.

pairing in figure 1, but one would not expect it at her intellectual level. There is, however, an adequate indication of slanting in figure 2. The clockwise rotation in figure 5 is not abnormal. Of course, the results would have been more convincing if this patient could also have been put through this test during the worst period of schizophrenic behavior, but there is no reason to doubt that she would have shown the same sort of dissociational disturbances that were found in all other schizophrenic subjects who were tested. Thus, it would appear that the schizophrenic dissociation in the sensorimotor patterns here examined is a reversible disturbance disappearing in connection with spontaneous remissions.

COMMENT

There have been previous publications on the drawings and artistic productions of schizophrenic persons, but no efforts at controlled studies or the copying of specific forms. Prinzhorn's [3] book is the best known, and a review of his illustrations gives some interesting confirmation of some of the principles brought out in this paper. No one example is better than the frontispiece (Der Würgengel), where the whole picture is composed of whirls and loops and radiating lines; the specific forms seem only partially evolved from this background and even the coloring seems only partially refracted light. Other productions by the same author in the text show the same principle. But the same thing is seen in many others also, especially in the so-called scribblings where the patient has filled a sheet of paper with loop-formed figures with the tendency from time to time to evolve some form, which may again be perseverated with gradual reduction of form to the background. Also in this book are many examples of the interesting distortions due to the rotation or disorientation of parts of figures. Thus, human forms may be drawn with one or more additional heads or other members, produced often at an angle to the first (or a rotational disturbance in a clockwise direction), each more vague or fragmentary than the preceding one. Then there is a tendency to perseverate such drawings again and again, each time with a greater distortion than in the former. If the intermediate stages are omitted, the final picture may be hard to analyze. Or a series of birds or other animals are drawn as though in a pattern about a radial axis, and the position of the birds is sometimes changed a little, or they are indefinite or fragmented. Designs showing such things as these are also common in primitive art, Oriental rugs, etc.[13]

The copying here reported, of the simple Gestalten by feebleminded persons seems to offer some suggestions about the genetic development of the visuomotor patterns, which are in keeping also with other studies made on children and in pathologic cases of different sorts. It thus appears that the more primitive sensorimotor patterns are dependent on the principles of constant motion, which seem to be largely a whirling movement in a vortex in clockwise and counter-clockwise direction, with an associated radiating directional component and with a tendency to emphasize horizontal planes. Fixed points are difficult to obtain, and straight lines are not accomplished as the shortest distance between two fixed points, but as an expression of the radiating tendencies. Parallel lines do meet before infinity, and crossed lines and angulated

13. Parkyn, Ernest A.: Introduction to the Study of Prehistoric Art, London, Longmans, Green & Company, 1915. Elliot, G. F. S.: Prehistoric Man, London, Seeley, Service & Company, 1917.

forms present great difficulties. There is always added to the radiating lines and planes, whatever may be its use or expression, the tendency for whirling in clockwise or counter-clockwise direction. The first evidence of expressed form, as shown at the second year level, is seen as little units of whirls or loops that are perseverated most freely in the horizontal plane in a dextrad direction. This may be largely a motor expression. In the perseveration of the loops, there is a slight constant variation from one to the next, a part of the time deviating away from the simple loop and then returning to it again. Series of such horizontally produced loops may be reduplicated, not in parallel formation, but always showing radiation and the tendency to curve. Some tendencies for Gestalt are seen at the 3 year level. These were rectangular forms either near to each other or inside one another. But some of the Gestalt principles are functions of the more highly elaborated perceptional motor capacities and only appear at the higher intellectual levels. Above 3 years, there is the tendency to accentuate the horizontal base line, to control perseveration and to produce wavy lines instead of broken ones for the representation of straight lines, and some effort to cross lines. At the 5 year level, there is a tendency to reduce the primitive loops to points, but this tendency is reversible even at the superior adult level, and there is a tendency to make straighter lines and better recognized Gestalten. At the 7 year level, there is a swinging back and forth between loops and dots, a capacity for many vertical and geometric Gestalten determined on the principle of internal organization and for crossed forms. At the 8 year level, most Gestalten forms are satisfactory; slanting forms are recognized, but their relations to the whole figure are not always possible. Pairing determined by slight differences is not possible. The major difficulty at this level seems to be in connection with the relations of parts to wholes. These things are satisfactorily accomplished above the 10 year level, though even then there is a certain amount of variation in individual cases. And at all levels all of the original principles are in evidence and tendencies to revert back to them are always present. Thus, there is always the tendency for dots to become loops, for straight lines to curve a little, for parallel lines to radiate toward or away from each other. These are common experiences for all of us when writing under pressure or fatigue on unruled paper, and they are illustrated in every chart here (see especially charts 7 and 8 for subjects at the 10 year level and the mental age of the superior adult). In the same charts and many others are seen the clockwise movement in figure 5 and the difficulties in connection with crossing in figure 6. Above all, there is always the tendency for sensorimotor patterns to revert back to the more primitive principles and to express movement in some way.

The dissociation that occurs in schizophrenia in the optic motor patterns, as they are illustrated here, may be said to depend on the last expressed general tendency, but not by a simple reversion back to any one even level of development in any regular way. The general principles of the basic intellectual level of the given person are always retained, even in advanced schizophrenia, but there are dissociations due to reversions back to some one or other of the primitive principles in this or that part of the sensorimotor pattern. As it is here demonstrated, it may be expressed as a change in the rate or direction of movement in a part or a whole of the pattern in one or two basic directions. Thus, there may be a disorientation or spatial separation of a part by a movement in the radial direction on the horizontal plane (most often) or by a rotatory or vortical movement to an angle of 45 degrees. This may take place in some integral part of the picture, thus exaggerating the principles of Gestalt or totally disregarding such principles, or it may involve the whole of the figure (chart 4, figs. 3, 4 and 1). There are also tendencies to revert to other more primitive principles, such as by perseverations, carrying over from one form into the next, changing dots to loops, fragmentation, representing dotted lines as wavy lines, micropsia and accentuation of the horizontal plane, and to avoid crossed and angulated forms, as well as failure to integrate the whole field or properly relate some one or more parts to the whole.

It may be said that movement, probably vortical, is the basis of the sensorimotor pattern and that internally organized "Gestalten" arise from it genetically by a progressive organization in connection with the integrated intellectual functions, and in schizophrenia there is a dissociation due to a reversion back to the genetically more primitive tendencies, but in no regular way (so far determined) and often in only a part of the pattern and without disturbing the native constituents of the internal organization of the pattern as a whole.

REFLEX RESPONSE LATENCIES

IN MANIC AND DEPRESSIVE CASES OF THE CYCLOTHYMIC GROUP AND IN CASES OF CATATONIC STUPOR OF THE SCHIZOPHRENIC GROUP *

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AND
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In earlier experimentation [1] we adduced information supporting the generally accepted concept that retardation and facilitation of the higher neural correlation centers increase and decrease, respectively, the activities of the lower neural correlation centers. The results of one study [2] included the observation that in psychiatric cases hyperfunction and hypofunction of the thought processes were associated, respectively, with hypofunction and hyperfunction of the patellar tendon reflex arc. The search for further confirmation or refutation of this observation led to the present study. The well known antithetical phases of the cyclothymoses, presenting on the one hand ideational flight and on the other hand thought retardation, seemed to offer ideally sharply contrasting degrees of activity of the neurologic hierarchies for the further testing of our observation.

From the total hospital population (1,600) were selected all of the frank manic and depressed patients whose cases were uncomplicated by any concurrent illness. At the particular season when this study was made, there were available eighteen frank manic cases and eight frank depressed cases. The small numbers of both groups can be

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* From the Psychopathic Hospital, Ann Arbor, and the Psychopathic Hospital, Iowa City.

* Permission was obtained from Dr. M. C. Mackin, Superintendent of the Mount Pleasant State Hospital, Mount Pleasant, Iowa, through Dr. Andrew H. Woods, Director of the Iowa State Psychopathic Hospital, to establish our laboratory in the Mount Pleasant State Hospital.

1. Travis, L. E., and Dorsey, J. M.: Effect of Alcohol on the Patellar Tendon Reflex Time, Arch. Neurol. & Psychiat., **21**:613 (March) 1929; Patellar Tendon Reflex Time in Psychiatric and in Neurologic Cases, ibid. **22**:99 (July) 1929. Dorsey, J. M., and Travis, L. E.: Effect of Alcohol on the Patellar Tendon Reflex Time in Dogs, ibid. **24**:48 (July) 1930.

2. Footnote 1, second reference.

explained by our insistence on the selection of pure cultures, as we felt that the statistical undesirability of the small numbers was offset by the truly paradigmatic nature of the cases selected. It should be added that, as is commonly observed in larger state hospitals, such as this one, the manic phase of the disorder was represented by hypomanic syndromes; likewise, the depressed phase of the disorder was represented by the syndromes of moderate depression. Because the cyclothymic depressions were not initially profound and were later perceptibly lifted by the experimental situation, in order to insure our obtaining records in which the activities of the higher levels were appreciably reduced we also selected five cases of classical catatonic stupor of the schizophrenic group. Of the total number of thirty-seven patients selected, eighteen women and thirteen men, ranging in age from 19 to 65 years, yielded readable records. As in our earlier work, we determined the reflex response latencies with the action current technic.

Group Comparisons

Group	Mean H/T	Range H/T
Manic	7.99 ± 0.05	7.26 — 8.60
Depressive	8.52 ± 0.06	8.00 — 9.24
Normal*	8.76 ± 0.02	7.88 — 9.93
Catatonic	13.67 ± 2.40	9.04 — 27.60

*This group is taken from the report of Travis and Young (J. Gen. Psychol. **3**: 374, 1930). It consisted of records of 122 university students.

EXPERIMENTAL RESULTS

As was noted in a previous study [3] and is deserving of further stress, reflex time alone is not a comparative value. This is true because of the individual differences obtaining in the lengths of the reflex arcs. To be of comparative worth, such a value must involve both the reflex time and the distance traversed by the nerve impulse. Since standing height, (even more than length of the peripheral arc) correlates higher with reflex time than does any other single physical measurement, the ratio, height divided by reflex time (H/T), was chosen as the unit for group comparisons. (Since its first application [3] this ratio has proved to be a practical means for the comparative studies of both group and individual differences.)

It is to be observed that the smaller the H/T value, the longer is the reflex time. The accompanying table shows this value as varying in a decreasing order from the manic group through the depressive and normal groups to the catatonic group. Statistical treatment of

3. Travis, L. E., and Dorsey, J. M.: The Relationship of "Intelligence" and Reflex Conduction Rate as found in Hypophrenic Children, J. Exper. Psychol. **13**:370 (Aug.) 1930.

these differences shows that the mean H/T value for the manic group is significantly less than are the mean H/T values in the depressive and normal groups. The observed difference between the mean H/T values for the manic and depressive groups is 0.53 ± 0.078. It is noted that this difference is more than six times its probable error.[4] The observed difference between the mean H/T values in the manic and normal groups is 0.77 ± 0.055. This difference is fourteen times its probable error. Approximately one half of the manic cases showed H/T values lower than the lowest normal H/T value (7.88) and all manic cases showed H/T values lower than the normal mean H/T value. Attention is called to the fact that all of the H/T values in the depressive group fall within the intranormal range of H/T values. After determining the standard deviation of the distribution of the H/T values for 122 normal persons reported by Travis and Young, we found the mean H/T value for our manic group to be two standard deviations removed from the normal mean.

Particularly impressive is the mean H/T value for the catatonic group, in that it is much higher than that for any of the other groups. There is not only no overlapping of the ranges of the H/T values in the catatonic and manic groups but only very slight overlapping of the ranges of the H/T values for the catatonic and the depressive and normal groups. Finally, it is observed that the mean H/T value for the catatonic group is 12.6 standard deviations removed from the mean for the normal group.

COMMENT

The results of this experimentation are in keeping with the results and strengthen the interpretations of our previous work. We found in the manic patients, as contrasted with both the depressive and normal patients, that inordinate activity of the higher neural levels is accompanied by reduced activity of the lower neural levels. The latter is manifested by the observed decrease in the H/T value and the implied decrease in the reflex conduction rate under conditions of superstructural overactivity. The fact that the mean H/T value and reflex rate were even slightly lower for the depressive than for the normal group calls for some explanation. We believe this explanation to lie partly in the noted fact that the constituents of the manic group deviated relatively further from normal behavior than did those of the depressive group. Especially was this true in the experimental situation which tended to excite both groups and thus disturb preexisting relationships between the two. Another explanation that can be con-

4. An observed difference is considered statistically significant if it is but three times its probable error.

sidered is that the activities associated with euphoric reactions may directly involve the higher levels more than do those associated with the depressed reactions.

The overlapping of the ranges of the H/T values for the manic and depressive groups, as well as the inclusion of all of the values for the depressive group in the range of H/T values for the normal group, is leading in the direction of another broad concept. It is an apparent truth that in both phases of the cyclothymic disorder not only the upper neurologic levels but the entire economy of the subject are affected. Viewing the problem ontogenetically, the fact that the higher and more recently acquired levels of the nervous system are less stable (less able to resist disorder) than are its lower and earlier acquired levels may account for the relative differences of activity obtaining in a disorder supposedly involving the bulk of the organism.

The inordinately reduced activity of the higher neural levels in patients with catatonic stupor was accompanied by abnormally increased activity of the lower neural levels. The latter is manifested by the observed increase in the H/T value and the implied increase in the reflex conduction rate under conditions of superstructural reduced activity.

SUMMARY AND CONCLUSIONS

From a study of the electromyographically determined patellar tendon reflex response latencies of manic and depressive patients, schizophrenic patients with catatonic stupor and normal persons, we arrive at the following conclusions:

1. In manic patients the reflex conduction rate is decreased over that of the normal subject.

2. In depressive patients the reflex conduction rate is within the intranormal range. An attempt has been made to understand this apparent inconsistency.

3. In schizophrenic patients with catatonic stupor the reflex conduction rate is greatly increased over that of the normal subject.

4. Our results generally tend to substantiate the concepts of neurologic dominance and of relative instability of more recently acquired neural levels.

CEREBROSPINAL FLUID IN DIFFERENTIAL DIAGNOSIS OF BRAIN TUMOR *

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Lumbar puncture in patients with marked choked disk is dangerous, especially in cases with subtentorial tumor. In such cases combined ventricular and lumbar puncture [1] is safer and gives added information. In doubtful cases with only slight or questionable choking of the disk, lumbar puncture, cautiously performed, is safe.

The cerebrospinal fluid pressure should be measured with a water manometer, the patient lying comfortably in an exact horizontal position. Procaine hydrochloride anesthesia should be used to avoid pain. A true pressure reading can be obtained only when the patient is fully relaxed. A false high pressure is most often due to emotional or physical tension. If the pressure is elevated, at least five minutes must be allowed for the patient to relax before a high pressure reading may be accepted as significant. Morphine and ether anesthesia raise the cerebrospinal fluid pressure.

A false low pressure may be caused either by dehydration due to catharsis, diarrhea or excessive vomiting, or by obstruction to free communication between the lumbar manometer and the ventricular fluid. Jugular compression should always be performed to test this communication, which may be completely or partially interrupted by a nerve root obstructing the tip of the needle, by a spinal subarachnoid block due to a spinal cord tumor, adhesive meningitis, etc., or by a tumor of the posterior fossa or the third ventricle. If jugular compression fails to give a prompt rise in the lumbar manometer, abdominal compression should be tried. If abdominal compression fails to give a prompt rise, the needle is not properly in place or is obstructed by a nerve root. Prompt response to abdominal compression gives assurance that the lumbar manometer

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1. Fremont-Smith, Frank, and Hodgson, J. S.: The Human Cerebrospinal Fluid, in Combined Ventricular and Lumbar Puncture in the Diagnosis of Brain Tumor, New York, Paul B. Hoeber, Inc., 1926, chap. 12.

Cerebrospinal Fluid in Differential Diagnosis of Brain Tumor *

Disease	Pressure: Mm. of Spinal Fluid Horizontal Position	Rise on Jugular Compression	Appearance	Cells per C.Mm.	Protein Mg./100 Cc.	Sugar Mg./100 Cc.	Chloride Mg./100 Cc.	Comment Heavy Type Indicates Findings Most Important in Differential Diagnosis
Normal: Lumbar Cisternal Ventricular	70-200	Prompt	Clear Colorless No Clot	0-5 0-5 0-3	15-45 10-25 5-15	50-75 50-75 55-80	430-455 (710-750 as NaCl)	Sugar and chloride values apply to fasting persons with normal plasma values. Normal values for urea nitrogen: 5-20 mg./100 cc.; for nonprotein nitrogen: 10-35 mg./100 cc. Globulin usually parallels protein content. Colloidal gold reaction is so variable it has little diagnostic value except where indicated below.
Brain tumor	**+**	N or delayed	N or yellow	Rarely increased	N or +	N or +	**N**	**Pressure nearly always increased.** Occasionally normal after catharsis or marked dehydration. See below.
Brain abscess	**+**	See brain tumor	Clear and colorless to turbid clot ±	**+**	**Slight increase**	**N or +**	**N**	**Pressure high. Polys nearly always present.** Chlorides may be low if complicated by high fever. Brain abscess represents one form of "Aseptic Meningeal Reaction." Extradural abscess and lateral or cavernous sinus thrombosis give similar picture. The cell count may be only slightly increased or several thousand per c.mm. In the latter case distinguish from purulent (bacterial) meningitis by normal or only slightly lowered sugar value. In purulent meningitis the sugar is nearly always below 40 mg. per 100 cc. Subacute bacterial endocarditis with emboli to brain may cause increased pressure, cells (polys) and protein.
Tuberculous meningitis	**+**	N	Opalescent to turbid faint yellow ± **delicate fibrin web**	+ Mononuclears	**+**	**Decrease**	**Marked decrease**	**Chlorides nearly always below 390 mg. per 100 cc.** (644 as sodium chloride). **Progressive fall in sugar** (occasionally high at outset). Occasionally very early in disease and in infants polymorphonuclears predominate. Tubercle bacilli may be found in clot or sediment. Guinea-pig inoculation positive.
Epidemic encephalitis	**N**	N	**N**	**N or slight increase no polymorphonuclears**	**N or slight increase**	**N or slight increase**	**N**	**Sugar is normal unless blood sugar is elevated. Cell count rarely exceeds 60. Over 50 per cent of cases have normal cell count. Protein increase when present is slight—rarely reaching 100 mg./100 cc.**
Meningovascular and parenchymatous syphilis	±	N rarely delayed	N Rare fibrin clot	+	+	N	N	**Wassermann reaction nearly always positive in lumbar fluid, but may be negative in ventricular fluid.** **Colloidal gold reaction nearly always in paretic or tabetic zone.**
Acute syphilitic meningitis	**+**	N	Clear to turbid faint yellow ± fibrin clot	+	+	**N or slightly low**	**Slightly low**	**Chloride higher than in tuberculous meningitis; nearly always above 400 mg. per 100 cc.** (660 as sodium chloride). **Wassermann reaction nearly always positive.**
Cerebral arteriosclerosis and arterial hypertension	Usually normal	N	N Occasionally slightly yellow	N or sl. +	N or +	N	N	**Pressure usually normal** even with extreme arterial hypertension. With cardiac decompensation and high venous pressure cerebrospinal fluid pressure will be high. Occasionally these cases have unexplained high intracranial pressure with choked disk and are extremely difficult to differentiate from brain tumor.
Uremia	**+**	N	N Occasionally slightly yellow	N or sl. +	N or +	+	±	**Urea and nonprotein nitrogen increased.** Chlorides often low if there has been much vomiting; sugar high because of hyperglycemia. Colloidal gold may show paretic curve. Occasionally cells or protein may be slightly increased and slight yellow color may be present.
Subdural hematoma	**+**	N	**Yellow or N**	**N** occasionally few red blood cells	**N or Sl +**	N	N	**All tubes equally bloody. Does not clot. Yellow tint to supernatant fluid within four** *A yellow fluid under increased pressure with normal or only slightly increased protein rarely occurs in any other condition.*

	Subarachnoid or ventricular hemorrhage	+	N	Bloody; supernatant yellow	+	+	N	N	All tubes equally bloody. Does not clot. Yellow tint to supernatant fluid within four hours after hemorrhage. This increases for eight to ten days until all red cells have disappeared. White blood cells often increased in fluid; at first, polymorphonuclears; later, mononuclear cells. When blood disappears pressure becomes normal. If bleeding due to tumor, pressure remains high.
	"Bloody tap" normal fluid	N	N	Bloody; supernatant clear	+	±	N	N	Variation in amount of blood in different tubes. If much blood present clot will form. Supernatant fluid clear and colorless, or pink if hemolysis has taken place; never yellow.
	"Epilepsy"	N	N	N	N	N	N	N	Normal fluid. Protein occasionally slightly increased.
	Myxedema	+	N	N	N	+	N	N	Usually mild tabetic colloidal gold reaction. Pressure, protein and colloidal gold reaction return to normal under thyroid therapy.
	Multiple sclerosis	N	N	N	±	±	N	N	A strong paretic or tabetic colloidal gold reaction in presence of negative Wassermann reaction in patient not previously treated for syphilis is strong evidence for multiple sclerosis.
	Lead encephalopathy	+	N	N or slightly yellow	+	N or +	N or +	N	Cells nearly always increased, occasionally up to several thousand—chiefly lymphocytes. Occasionally polymorphonuclears predominate especially in children. Pressure nearly always elevated. Lead is present in cerebrospinal fluid.

COMPARISON OF LUMBAR AND VENTRICULAR FLUID IN BRAIN TUMOR

Above Tentorium	Not Involving Wall of Ventricle	Lumbar	+	N	N	N	N or slight increase	N or +	N	Above Tentorium: Pressure nearly always increased. Ventricular fluid normal unless tumor invades wall of ventricle when protein will be increased in fluid from that ventricle and in lumbar fluid. The uninvolved ventricle may have normal fluid. A tumor involving the subarachnoid surface of brain may give increased protein in lumbar fluid but ventricular fluid is normal. Xanthochromia sometimes present when protein is increased. A degenerating tumor involving wall of ventricle may give cellular increase both in ventricular and lumbar fluid. Rarely polymorphonuclears predominate. A degenerating tumor involving subarachnoid surface of brain may give increase in cells in lumbar fluid, but not in ventricular fluid. Tumors of optic chiasm may cause mononuclear cell increase in lumbar fluid. Leukemic tumors may cause increase in lymphocytes. Tumor of third ventricle may give increased protein in both lumbar and lateral ventricular fluid, and a delayed response to jugular compression in lumbar manometer. A bleeding tumor gives hemorrhagic fluid like subarachnoid hemorrhage (see above). Pressure remains high after bleeding ceases. Protein may be excessively high for amount of blood present.
		Ventricular	+	N	N	N	N	N or +	N	
	Involving Wall of Ventricle	Lumbar	+	N	N Occasionally faintly yellow	N or slight increase	+	N or +	N	
		Ventricular	+	N	N Occasionally faintly yellow	N or slight increase	+	N or +	N	
Below Tentorium	Intracerebellar and Fourth Ventricle	Lumbar	+	N or delayed	N	N	Slight increase or N	N or +	N	Below Tentorium: Pressure nearly always increased. The ventricular fluid is normal. The lumbar fluid may be normal or show increased protein and sometimes xanthochromia. Acoustic neuromas nearly always cause a definite increase in protein in the lumbar fluid. Cerebellar tumors may produce no increase or a slight increase in protein in the lumbar fluid. Tumors of the fourth ventricle usually produce no abnormality in the lumbar or ventricular fluid. Tumors below the tentorium often produce a partial "subtentorial block" so that the response to jugular compression is delayed in the lumbar fluid. Glioma of pons may give normal pressure, normal protein, and normal response to jugular compression. Polyneuritis (etiology unknown) occasionally gives choked disk, with high pressure, marked increase in protein and sometimes yellow color. Lumbar puncture in patients with choked disk may be dangerous unless the ventricle is tapped at the same time.
		Ventricular	+	N	N	N	N	N or +	N	
	Extracerebellar	Lumbar	+	N or delayed	N or faintly yellow rare clot	N	+	N or +	N	
		Ventricular	+	N	N	N	N	N or +	N	

communicates freely with the lumbar fluid. When the spinal subarachnoid space is blocked by a tumor, Pott's disease or adhesions, abdominal compression gives a more prompt and more marked rise in the lumbar manometer than does the jugular compression.

A brain tumor nearly always causes increased cerebrospinal fluid pressure unless the patient has been dehydrated. The pressure is often elevated for several months before the disks become choked. Very early tumors, infiltrating gliomas of the pons and pituitary tumors that remain within the sella turcica may give normal cerebrospinal fluid pressure.

Abstracts from Current Literature

REPORT OF THE FIFTH CONGRESS OF SCANDINAVIAN NEUROLOGISTS, STOCKHOLM, 1930. Acta psychiat. et neurol. **6**:127, 1931.

The first day's session was devoted to a consideration of epilepsy. Abstracts of the papers presented in this symposium follow, with the exception of three papers that were published in other journals as indicated:

1. THE PATHOLOGIC ANATOMY OF EPILEPSY. H. MARCUS, Finska läk.-sällsk. handl. **73**:335, 1931.

2. HYPERVENTILATION EXPERIMENTS DURING CARBON DIOXIDE AND OXYGEN INHALATION ON PATIENTS SUBJECT TO CRAMPS. M. FOG and M. SCHMIDT, J. Neurol. & Psychopath. **12**:14 (July) 1931.

3. EPILEPSY AND MARRIAGE. BROR GADELIUS, Hygiea **93**:98 (Feb. 15) 1931.

THE CLINIC FOR EPILEPSY. G. H. MONRAD-KROHN, Acta psychiat. et neurol. **6**:137, 1931.

The author points out that the problem of epilepsy is far from being solved. Experiments have failed so far to produce anything that can justly be called epilepsy. Anatomic research has brought no solution of the question. The author's purpose was to discuss what contributions have emanated from clinical research. He objects to the terms "genuine," "idiopathic" and "essential" epilepsy as misnomers, preferring to call the epilepsies other than the symptomatic, cryptogenic. He states: 1. The clinical examination of epileptic patients between seizures shows nothing abnormal in the majority of cases. 2. As regards the mental state, nothing markedly abnormal is found. The peculiarities that are generally considered characteristic of epilepsy (namely, a pedantic, overcorrect attitude, a cantankerous disposition, a superficial religiosity) are absent in the majority of noninstitutionalized epileptic persons. 3. As regards the physical condition, there are highly varying statements in the literature. The author quotes the reports on two investigations of 300 epileptic persons in only 17 per cent of whom nothing was abnormal on neurologic examination. He believes that these statistics are instructive regarding institutionalized patients, but that in the noninstitutionalized epileptic person neurologic examination reveals abnormal signs in only from 2 to 3 per cent, and even these signs are often very vague. 4. No definite type of vegetative disturbance can be claimed to be peculiar to epilepsy. 5. No certain increase or diminution of any one of the normal substances of the blood has yet been demonstrated constantly to precede the seizures, but greater variations are found in epileptic than in other persons. 6. In some instances there has been found a preparoxysmal increase in weight; but it has not been constant, and in many cases it has been very slight, while on the other hand a more appreciable increase in weight often has occurred without a succeeding seizure.

The author then discusses the seizures themselves. After mentioning the various types of aura he concludes "in the semeiology of the epileptic aura there is hardly a feature which we do not know from the semeiology of cerebral tumor." This seems to indicate that the corresponding cerebral centers represent a locus minoris resistentiae to the epileptic attack. In view of this it seems probable that slight local changes of some kind are necessary to form a point of entry for the epileptic seizure. Although neurologic examination during the seizure is difficult and most fragmentary, the following findings may be claimed to be fairly well established: the pupillary light reflex cannot, as a rule, be elicited during the attack, and the same applies to the corneal and conjunctival reflexes; the abdominal

reflexes are sometimes abolished, sometimes not; sometimes, on account of twitchings, it is impossible to decide whether they are present or not; the cremasteric reflexes are sometimes absent, sometimes present; the deep reflexes are sometimes absent, sometimes present; a fairly constant feature is an extensor plantar response, which often also outlasts the attack by some minutes; the conscious psychic continuity is always broken, but the superior psychic control is eliminated to a very different degree and the primitive impulses liberated to a corresponding degree; in other words, transitions from a low primitive state of uncontrolled impulses with homicidal possibilities to more orderly forms of peaceful automatism are met with. He is convinced of the existence of the pre-epileptic attacks reported by Levy and Patrick.

Monrad-Krohn's experiences with the hyperventilation method of eliciting an attack have been disappointing. In forty cases of cryptogenic epilepsy, ninety-one hyperventilation tests have been carried out, and of these only five (i. e., only 5.56 per cent of the total number of tests) have elicited a definite epileptic manifestation in addition to the quasinormal phenomena of tetany. In ten cases of symptomatic epilepsy, twenty hyperventilation tests have been carried out, with negative results in all.

As regards heredity, alcoholism and epilepsy in parents and forefathers have been considered of some importance, but the discrepancies between different statistical studies is too great to permit any conclusions. Epileptic attacks seem to be more frequent during the spring and early summer.

Although the onset of epilepsy frequently occurs about puberty, and although it is generally thought that epileptic attacks that start after the age of 30 are as a rule not due to cryptogenic epilepsy, it must be remembered that a case of nocturnal epilepsy, which may have started long before, may not be discovered till long after the age of 30, e. g., when the patient marries at that age.

Among predisposing factors may be mentioned emotional stress, lack of sleep, the ingestion of alcohol and sometimes of chocolate. Of preventive factors one of the most important is rest, and particularly rest in bed. Pregnancy entails both predisposing and preventive factors.

In regard to treatment, both the ketogenic treatment and the dehydration treatment have an interest far beyond their mere practical therapeutic results. With ketogenic treatment the author has had some encouraging results, with dehydration treatment, insufficient experience. Unfortunately, both kinds of treatment are so unpleasant to some patients that any attempt at carrying out the treatment has to be given up.

In regard to the etiology or pathogenesis of epilepsy, the following conclusions are suggested: (1) local cerebral or meningocerebral lesions play, or at least may play, a part; (2) metabolic disturbances resulting in some kind of accumulation (i. e., water retention) leading up to the paroxysmal manifestation probably play an important part in most cases; (3) vascular (vasomotor?) disturbances may also play an important part; (4) external conditions also have a decided influence (the relation between rest and fatigue is here of prime importance), and (5) in a few cases, ingestion of some substances calls forth attacks, probably by way of an anaphylactic shock mechanism.

Clinical observations show an overwhelming probability of a number of different causative factors entering into play.

PEARSON, Philadelphia.

THE PATHOPHYSIOLOGY OF EPILEPSY. H. P. STUBBE TEGLBJAERG, Acta psychiat. et neurol. **6**:159, 1931.

The pathophysiology of cryptogenic epilepsy is discussed in two parts, the pathologic observations during the paroxysm (particularly in the preparoxysmal period) and in the intervals.

At the beginning of the seizure there is an abrupt fall in the pressure of the cerebrospinal fluid, probably due to the reduced volume of the brain. During the further course of the seizure, the pressure rises simultaneously with an

increase in the pressure of the veins, caused by the apnea. In 60 per cent the cell count of the cerebrospinal fluid is within normal limits, and the albumin content, globulin and calcium are within normal limits. Although other investigators have found a normal percentage relation between the sugar of the blood and that of the spinal fluid, the author found this relation increased in fourteen of thirty-six cases. Immediately before the seizure there is an increase in the systolic blood pressure of about 30 per cent, while the diastolic blood pressure is influenced only to a slight degree. In the intervals, the blood pressure seems to be more labile than usual, but within the limits of normal.

The results of investigations on the sedimentation reaction, viscosity, coagulation and hormone contents of the blood were conflicting, but on the whole they showed a greater variability then is found in normal persons. Examinations of the blood sugar during fasting have shown normal conditions. The blood sugar curve after ingestion of dextrose was normal in most cases, but latent diabetic types were found in about 25 per cent. On administration of dextrose and after injection of epinephrine, the sugar threshold of some epileptic persons has shown variations, and in a few cases there has been a difference in the threshold after the administration of dextrose and after the injection of epinephrine. Variations in the amount of urine in connection with the epileptic fits, taking the form of a preparoxysmal oliguria and a postparoxysmal polyuria, are well known clinical facts, and they constitute the essential cause of the variations in body weight that have been observed in connection with the seizure. None of the observations of paraxanthin, phosphorus, sulphur, uric acid, etc., have turned out to be specific to the epileptic organism or the epileptic seizure. Epileptic persons show a great variability in the numeral values of p_H and ammonia, but without this being pathognomonic of epilepsy, as it is found also in degenerates, in a few psychotic patients and in some normal persons. Examination of the effect of parathyroid extract on six epileptic persons showed no result.

In regard to the evidence of disorders in the endocrine system, the author states that examination of the basal metabolic rate in a considerable number of cases of epilepsy showed partly spontaneous variations in each single case, partly a considerable number of subnormal values and a few values above the normal. The main evidence of a dysfunction of the parathyroid glands—changes in the calcium metabolism—is by no means a definite symptom in epilepsy, as both the total calcium and the ionized calcium of the blood serum have normal values, even though in persons with epilepsy the values are placed around the lower normal limit, and the individual variations are larger than in normal persons.

In regard to the possibility of a connection between the seizures and the acid-base balance, the actual p_H in epileptic persons varies from 7.26 to 7.52. The investigations on hyperventilation and the epileptic fits caused thereby prove that neither disturbances in p_H nor in the alkali reserve are sure to cause convulsions, and it seems as if the effect of hyperventilation is due to an anoxemia.

The author believes that the most fruitful fields of research in epilepsy will be investigations on the colloids of the blood, the permeability of the tissues and the condition of the blood vessels, particularly the capillaries. He concludes that the pathophysiologic conditions in epileptic persons indicate that there is a disturbance in the function of the central nervous system, the so-called decreased threshold for convulsions. Furthermore, many factors show that a labile and in certain respects abnormal metabolism is necessary to the provocation of the epileptic syndrome. Whether the latter is of neurogenic origin, or whether the cerebral factor, which is called the decreased threshold for convulsions, has developed on account of disturbances in the metabolism, only the future may show.

PEARSON, Philadelphia.

THE TREATMENT FOR EPILEPSY. H. I. SCHOU, Acta psychiat. et neurol. **6**:177, 1931.

The author concludes that, apart from surgical measures, the treatment for epilepsy is still symptomatic. Phenobarbital is the best drug and ought to replace

bromides partially or altogether. Treatment by diet is uncertain, and the therapy needs more experimental research. Starvation treatment is useful in severe cases. In status epilepticus a barbital derivative should be used. The social treatment is extremely important.

PEARSON, Philadelphia.

THE SURGICAL POINT OF VIEW IN THE TREATMENT FOR EPILEPSY. H. OLIVECRONA, Acta psychiat. et neurol. **6**:193, 1931.

The author discusses the use of surgical methods of treatment in cryptogenic, traumatic and jacksonian epilepsy. He mentions the numerous surgical procedures advised in the first type, and draws attention to the well known fact that improvement often follows any one of them. Such methods, of course, show greater results when adopted soon after the onset of the symptoms. He does not think that extirpation of various parts of the cortex, as advised by Foerster, is supported by any rational basis, nor does it have any distinct therapeutic value. He concludes that the surgical treatment for true epilepsy still is in an experimental stage. For traumatic epilepsy resulting from a nonlocalized or nonlocalizable lesion, surgical treatment holds no benefit, except when there is clear evidence of difficulty in cerebrospinal circulation. In the latter case decompression is of value. Even if the lesion is localizable, the case should be considered carefully before surgical intervention is attempted. Even if the lesion is a scar, extirpation of this scar may result only in the formation of a new one, with no improvement in the patient's general condition. The results of surgical treatment in traumatic epilepsy at best are not very encouraging.

Operation in cases of jacksonian epilepsy is determined by the nature of the lesion. If the attack is followed by temporary paresis, exploration is probably advisable. If the paretic signs do not follow, it is better to adopt an expectant attitude. The author is very doubtful as to the value of cortical excisions in jacksonian epilepsy.

PEARSON, Philadelphia.

CLINICAL AND THERAPEUTIC EXPERIENCES WITH EPILEPSY. R. FORSBERG, Acta psychiat. et neurol. **6**:207, 1931.

The author reports briefly his experiences with hyperventilation and a ketogenic diet in epilepsy. In five of forty-five cases of cryptogenic epilepsy, hyperventilation produced a convulsion. (This is 17 per cent of the number of cases, but only 6 per cent of the number of experiments.) In thirteen cases of symptomatic epilepsy, hyperventilation did not produce an attack. A ketogenic diet was tried in eight children with cryptogenic epilepsy and in one child with pyknolepsy. It was possible, however, to keep only one child on this diet for a long period (a year); he recovered from the attacks and has remained free for a year following the cessation of treatment. Another child remained on the diet for eighty-five days, and the number of attacks was reduced from twenty to two a month. Two children showed no benefit after from four to six months' trial of this method. Another child improved while on the diet. The patient with pyknolepsy showed no improvement during a two month period.

PEARSON, Philadelphia.

ORGANIC SYMPTOMS FROM THE CENTRAL NERVOUS SYSTEM IN SO-CALLED GENUINE EPILEPSY. H. P. STUBBE TEGLBJAERG, Acta psychiat. et neurol. **6**:209, 1931.

The author reports briefly the clinical neurologic observations in 346 cases of epilepsy. Of these, 81 (i. e., 25 per cent) showed symptoms of an organic nervous disease, which, according to the case history, had developed either previous to or simultaneous with the first epileptic seizure. Six patients had had poliomyelitis, encephalitis and the like, which had developed after the commencement of the epilepsy, and 5 had unspecific neurologic symptoms, ascertained before the admission of the patient but after the first seizure. One hundred and ten patients

(i. e., 32 per cent) showed organic neurologic abnormalities of a diffuse or atypical nature; 133 patients (i. e., 38 per cent) showed a pathologic condition of the spinal fluid; 69 patients (i. e., 20 per cent) showed more or less pronounced symptoms of endocrine disturbances, and only 20 of the 346 patients (i. e., 6 per cent) showed no neurologic abnormalities.

Among the 81 patients with organic nervous diseases, which had developed before the epilepsy, were 16 patients with congenital cerebral diseases, 14 with encephalitis infantilis or epidemica, 13 with poliomyelitis or sclerosis disseminata, 27 with contusions or commotio cerebri, 2 with arteriosclerosis cerebri, 2 with chronic alcoholism, 11 with congenital syphilis and 1 with tumor cerebri. In a number of cases he found anomalies of pigmentation, particularly "brun pandering" (brown brow-ring). In his opinion the most probable explanation of this dyschromia faciei is a disturbance of the central vegetative system, and he believes that these cases ought to be considered as connected with hydrocephalus internus, which has produced a pressure on the area around the floor of the fourth ventricle.

PEARSON, Philadelphia.

BIRTH TRAUMA AND EPILEPSY. E. RYDBERG, Acta psychiat. et neurol. **6**:213, 1931.

The author has studied the lives of forty-nine children who showed definite evidence of intracranial trauma at birth and who are now at least more than 2 years of age. He reports in detail two cases in which there later developed convulsive seizures. He classifies the forty-nine patients as follows: (1) idiots and imbeciles (including 12 epileptic patients), twenty; (2) epileptic persons without defective intelligence, six (five?); (3) patients with spastic paralysis without defective intelligence or epilepsy, two; (4) infants with disturbances affecting the neuromuscular apparatus of the eyes, but without other defects, seven; (5) infants who died so early that nothing was known of the extent of the injury, two; (6) infants who died at a very early age, but in whom epileptic attacks had already occurred, two, and (7) healthy infants, ten.

It will be noticed that twenty infants had epileptic attacks. These attacks are often of the jacksonian type, or are characterized by the fact that the cramps are localized. Cases occur in which the convulsions are general, as well as those accompanied by fits of unconsciousness without convulsions. Aura and petit mal have been mentioned in one or two cases. This form of epilepsy has the general characteristics of what is known as secondary epilepsy. However, although local signs of cranial injury may not be pronounced, the author believes that even in cases in which the convulsion is general there are features that distinguish this form of disease from "genuine epilepsy." A characteristic feature of the latter disease is a brief period of convulsions followed by deep coma. Traumatic epilepsy, and even that produced by a birth trauma, is characterized by the fact that the attacks are frequently of much longer duration; in some of these cases, for instance, they have lasted for hours. Even during severe attacks the patient may retain consciousness and afterward remember the attack. If it is added that most patients with epilepsy due to a birth injury show other defects that can be traced back to a very early age, it is obvious that in its essential features and in the great majority of cases this form of disease differs from primary epilepsy. Of the twenty cases in which epileptic fits occurred, there is not one that has presented such symptoms as would lead a physician to diagnose it as a case of genuine epilepsy, even if he were not aware of the existence of a birth injury.

PEARSON, Philadelphia.

CELL COUNT AND PROTEIN CONTENT OF THE SPINAL FLUID IN EPILEPSY. AXEL V. NEEL, Acta psychiat. et neurol. **6**:221, 1931.

The author attempted to correlate the spinal fluid findings in 381 cases of epileptiform convulsions, with the aim of elucidating to what extent one may ascertain the cause of the epilepsy in any particular case by an examination of

the spinal fluid. He divided the cases into two main groups: I, in which examination did not reveal any definite cause for the convulsions, and II, in which the symptoms were suggestive of such a cause. In group I the total protein content falls very evenly around the dilution value 6, whereas in group II a very large number of cases show an increase in the total protein content. As a rule, there is no marked increase in globulin in either group. The cell count is higher in group II than in group I. The main result of this study showed that the spinal fluid is normal in the forms of epilepsy in which there is no demonstrable external cause, normal even to the strictest requirements. Quite the opposite applies to group II.

If the cases of group I are tabulated according to the number of years the disease has lasted, the moderate pathologic changes are somewhat more frequent in old cases, with a duration of illness of thirty years or more, than in cases of from ten to fifteen years' standing. On the other hand, in old cases with pronounced psychic changes, the spinal fluid is often perfectly normal. Cases of recent origin, with a duration of the illness for six months or less, show relatively slight changes.

He concludes that one is justified in claiming that by examination of the cell count and the protein content of the spinal fluid one may obtain some important data for the estimation of a case of epilepsy. If one finds the spinal fluid perfectly normal, this will suggest strongly that there is no organic brain lesion. When, on the other hand, a change is demonstrated, it would be a sure indication of the presence of an organic brain lesion, so that such a case of epilepsy, as a rule, would have to be considered symptomatic.

PEARSON, Philadelphia.

THE PHYSIOLOGIC AND CHEMICAL BASIS OF STARVATION. CARL CLEMMESEN, Acta psychiat. et neurol. **6**:233, 1931.

The basal metabolic rate of sixteen epileptic patients during and after from ten to twelve days of starvation treatment showed an average increase of 6 per cent, and after that a proportional and continuous fall. Acetonemia did not seem to raise the basal metabolic rate. In eighteen epileptic patients the blood sugar fell in the first four days from 85 to 61 mg., and then rose without reaching normal limits. No symptoms of hypoglycemia occurred. Acetone in the blood in six patients increased during the first six or seven days of starvation and then remained stationary.

PEARSON, Philadelphia.

THE SUGAR CURVE IN THE CEREBROSPINAL FLUID AFTER THE ORAL ADMINISTRATION OF DEXTROSE. AUDUN SCHJÖTT, Acta psychiat. et neurol. **6**:247, 1931.

The author studied 117 cases. Of these, 16 were cases of cryptogenic epilepsy. In all except the epileptic cases the increase of sugar in the spinal fluid began from one and one-half to two hours after the oral administration of dextrose; the increase continued and reached its maximum from two and one-half to three hours after the administration, whereupon followed a slow decrease to the original amount. In 13 of the 16 cases of cryptogenic epilepsy, there was an increase in the sugar of the spinal fluid, which greatly exceeded the increase found in all the other conditions, and which also began considerably earlier.

PEARSON, Philadelphia.

CONJUGATE DEVIATION OF THE HEAD AND EYES: ITS VALUE IN THE DIAGNOSIS AND LOCALIZATION OF ABSCESS OF THE BRAIN. I. LEON MEYERS, Arch. Otolaryng. **13**:683 (May) 1931.

Twenty-four cases of brain abscesses were confirmed by operation or post mortem. The diagnosis was made largely on objective observations, of which conjugate deviation was important. Conjugate deviation of the head and eyes is

found by stimulation of the following areas: 1. The presigmoid area in the dog and the posterior third of the middle frontal convolution in the ape. 2. The visual zone of the occipital lobe around the calcarine fissure in the monkey. The independence of this center from the frontal center has been demonstrated in the dog. 3. The first temporal convolution (the center of hearing). Munk contended that its destruction gives rise to a psychic deafness. Stimulation is followed by turning the head and eyes to the opposite side. 4. The parietal lobe in the region of the angular and supramarginal gyri. "It is evoked, according to Munk, on excitation of the visual zone, owing to the fact that excitation of this zone awakens in the animal a visual impulse from the contralateral field of vision, and the animal directs attention to it by turning the head and the eyes in its direction. Excitation of the parietal lobe similarly awakens a sensory impulse in the realm of general sensibility (touch, pain or muscle sense) on the opposite side of the body, causing the animal, in similar fashion, to look toward the point experiencing this sensation; the same is true in the case of stimulation of the auditory center. Ferrier accordingly considered the frontal area for conjugate deviation of the head and eyes as the motor center for voluntary movements of attention, the center of what Wundt designated as aperception."

The exact focus of irritation giving conjugate deviation in man is not definitely established. Only little electrical stimulation of the brain in man has been done. Conjugate deviation of the head and eyes, the result of destructive lesions, is better understood. In destructive lesions of the cerebrum, the head and eyes are turned toward the lesion. In destructive lesions of the cerebellum, conjugate deviation is toward the side opposite the lesion. Owing to the fact that tumors grow so slowly, they are not as satisfactory for localization as abscesses that form quickly and give an acute and more localized pressure.

Conjugate deviation can be determined by: (1) asking the patient to look to one side and the other, when it will be seen that on attempting to look in the direction opposite that of the deviation of the eyes, he is unwilling to move his eyes, but turns his head in that direction, exerting pressure on the examiner's hand, and (2) a marked persistence of the deviation of the head and the eyes as the slow component of nystagmus, when the latter phenomenon is evoked by stimulation of the labyrinth with the "cold caloric" on the side toward which the eyes deviate spontaneously, and the consequent delay in the development of the quick component to the other side.

In cases of supratentorial abscess, the observations were as follows:

Case 1.—There was slight but fairly noticeable conjugate deviation of the head and the eyes toward the side of the lesion in the case of a small, circumscribed abscess in the posterior part of the right frontal lobe, adjacent to the ascending frontal convolution.

Case 2.—There was extreme conjugate deviation of the head and the eyes to the side of the lesion in the case of an abscess in the region of the angular gyrus of the right parietal lobe.

In the cerebellum, the conjugate deviation is to the side opposite the lesion. Cerebellar stimulation results in deviation to the same side in the ape. Meyers believes that conjugate deviation to the side opposite from the lesion is cerebellar in origin, in contradistinction to Clark and others who have thought that the nuclei in the pons were affected. Conjugate deviation is independent of the direction of nystagmus. The deviation of the eyes is always to the side opposite the lesion. The nystagmus, i. e., the quick phase, may be in either direction. The deviation of the eyes in abscess of the cerebellum is also independent of the position of the head.

Case 3.—This case showed a small, circumscribed abscess within the lobulus quadrangularis of the left hemisphere of the cerebellum, close to the tentorium; conjugate deviation of the eyes to the right, and nystagmus, horizontal in type and small in amplitude to the right, with the head in midline.

CASE 4.—There was an arachnoid cyst, secondary to acute otitis media, in the inferior part of the right hemisphere of the cerebrum, with much destruction of cerebellar tissue, chiefly in the region of the digastric lobule in a child, aged 1 year. There were also conjugate deviation of the eyes to the left, horizontal nystagmus to the left, with none to the right, and extreme deviation of the head to the left.

CASE 5.—There was a large abscess of the right hemisphere of the cerebellum. When examined for the first time, the patient was in deep stupor. There was pronounced conjugate deviation of the eyes to the left; the head was deviated to the left, but there was practically no nystagmus.

CASE 6.—A small abscess, not yet encapsulated, was found in the region of the tonsil of the right cerebellar hemisphere. There were conjugate deviation of the eyes to the left, nystagmus to the right and deviation of the head to the right.

CASE 7.—An abscess of the left hemisphere of the cerebellum was found in a woman, aged 24. The right eye was deviated to the right; the left eye, owing to paralysis of the internal rectus muscle, was in the midline. The head tended to deviate to the left, offering resistance when it was passively turned to the right. There was no nystagmus.

CASE 8.—An abscess of the right side of the cerebellum was present in a woman, aged 25. There were conjugate deviation of the eyes to the left; no deviation of the head, and very slight nystagmus to the right, with none to the left.

CASE 9.—As evidenced by the clinical phenomena, there was an inflammatory, serous process of the right hemisphere of the cerebellum which subsided before going on to suppuration. The symptoms cleared up gradually, and the patient recovered without an operation.

CASE 10.—Circumscribed meningitis at the cerebellopontile angle on the right side was diagnosed; operation was performed, and the diagnosis was confirmed at autopsy. Deviation of the eyes to the left, the "skew" deviation, was found. Hearing was lowest in the right ear, and there were Bárány findings of cerebellopontile angle disease.

CASE 11.—F. C., a boy, aged 5 years, was admitted to the department of the hospital for contagious diseases on Dec. 27, 1930, with chickenpox and bilateral otitis media. A discharge from the ears was reported to have developed about a month before admission to the hospital. He contracted chickenpox a few days before admission, simultaneously with which the discharge from the right ear became profuse, and he began to suffer from severe headaches and vomiting. During the first week in the hospital, the temperature ranged from 100 to 101.6 F., and a simple mastoidectomy was performed on the right side on Jan. 4, 1931. During the week following, the temperature ranged from 101 to 103 F. It became subnormal (98.4 F.) on January 12, and the pulse rate dropped to 68.

After chickenpox and otitis media, the eyes showed conjugate deviation to the left with the head to the same side. The diagnosis was abscess of the cerebellum on the right side, and this was confirmed by operation.

Summary.—1. In abscess of the cerebrum, conjugate deviation of the head and eyes is extreme when the lesion affects the angular gyrus of the parietal lobe; it is of moderate extent if the lesion affects the posterior part of the frontal lobe close to the rolandic region. It is absent, no matter how extensive the lesion, in abscess of the prefrontal region of the frontal lobe, in abscess of the occipital lobe and in abscess of the temporal lobe. The deviation in cerebral lesions, when present, is toward the side of the lesion. Interpreting the movement as an attitude of attention, and assuming the angular gyrus to be the center of psychic vision (i. e., the interpretation of visual stimuli), as shown by the fact that lesions of this region on the left side give rise to alexia or agnosia, the inability to understand writing or to recognize objects by vision, I conclude that attention is dominated most powerfully by stimuli arising within the sphere of vision and relatively little by other kinds of stimuli.

2. Conjugate deviation of the eyes, regardless of the position of the head, is an invariable accompaniment of an abscess of the cerebellum. The deviation, varying in extent, in this type of case is in a direction opposite the lesion. It manifests itself most clearly as a persistent deviation of the eyes to the side opposite the lesion on cold caloric stimulation of the labyrinth on that side, the deviation interfering with or greatly delaying the development of the rapid phase of the nystagmus. The phenomenon is undoubtedly due to involvement of the cerebellum itself, and not to an involvement of structures at a distance.

3. In abscess of the cerebellum, the nystagmus is toward the side opposite the lesion, when the labyrinth on the side of the lesion is destroyed. It is toward the side of the lesion when the labyrinth is functioning. It may then be due to irritation of the labyrinth or to deficiency of the cerebellum.

4. Nystagmus may be slight or even absent in abscess of the cerebellum.

5. The deviation of the head that is frequently observed in abscess of the cerebellum corresponds in direction to that of the quick component of the nystagmus. It is suggested that the deviation of the head is a compensatory phenomenon intended to replace in part the movement of the eyes that is to occur during the slow component of the nystagmus, a movement which, as explained, becomes restricted in range, owing to the deviation of the eyes brought about by the lesion of the cerebellum.

This is an excellent article, concise and well written, and the argument is well sustained. It should be read in full.

HUNTER, Philadelphia.

OTITIC MENINGITIS. ALAIN GASTON, Rev. d'oto-neuro-opht. **9**:397 (June) 1931.

In the pathogenesis of otitic meningitis, the cerebrospinal fluid constitutes one stage in the bacterial invasion and also has a protective function. Originating in the choroid plexuses, it is absorbed by the venous sinuses of the skull through the intermediary of the venous network adjacent to the sheets of liquid covering the brain. These pools of liquid are separated from each other by a close network of subarachnoid tissue, the circulation of which is from the ventricles through the foramina of Magendie and Luschka to the cisterna magna; from there, three pathways are used: (1) through the sylvian canal to the pools over the hemispheres; (2) through the supracerebellar sagittal canal to the interhemispheric fissure, and (3) to the spinal canal. The first route is the most important. Otitic infection may be transmitted to the meninges by way of the bone (contiguity) or through the blood vessels. No lymphatic communication between the ear and the meninges has ever been found. Other pathways are the vestibular aqueducts. Localized inflammation of a venous wall is capable of infecting the spinal fluid without causing actual meningitis. This explains cases of purulent meningitis that are cured by repeated lumbar punctures. The frequency of meningitis in otology is the direct result of the absorption by the veins of an infected cerebrospinal fluid. An extended obliteration of the venous system of the endocranial surface of the petrous bone is a serious obstacle to drainage of the cerebrospinal fluid and, by inflammatory reaction, causes a hypersecretion. Cases of hypertensive meningitis are thus explained. Chronic otitic infections usually affect the meninges through the bony pathway. The infection being attenuated, meningeal adhesions arise, causing encysted meningitis. Acute otitis and acute flare-ups of chronic otitis reach the meninges by the vascular route and cause a generalized diffuse meningitis. The pools of fluid covering the hemispheres are independent of each other. This explains the paradoxic results often obtained from puncture of the cisterna and the fact that cerebrospinal fluid obtained by lumbar puncture does not always indicate exactly the changes that have occurred.

The variability of the signs and symptoms of a meningeal complication makes a precise diagnosis and prognosis difficult. The problem rests on four fundamental elements: (1) the etiologic factors, (2) the clinical signs, (3) the operative findings

and (4) a study of the cerebrospinal fluid. Acute meningitis, occurring in the first days of acute otitis or during certain epidemics of grip, is caused by the invasion of bacteria through vascular channels. Acute early labyrinthitis ends in meningitis in one fifth of the cases. Late labyrinthitis, if let alone, causes meningitis in two thirds of the cases. When labyrinthitis is present, search must be made for the first signs of meningeal irritation (dull headache, stiff neck, suggestion of Kernig's sign) and, especially, slight changes in the spinal fluid. Meningitis following operative intervention is almost always diffuse and of grave prognosis. The complete syndrome of meningitis has a very grave prognosis, particularly when localizing signs are present. Persistence of consciousness is a favorable indication, as is improvement after operation on the auricular focus. Localized meningitis is much less serious. Observations at operation on the mastoid process give valuable prognostic data.

The clinical diagnosis and the results of examination of the cerebrospinal fluid are often in accord, but not always. In France, suboccipital puncture is preferred to lumbar puncture but, except in the cases resulting from labyrinthitis, there is not much choice between them. By their use in certain cases of acute labyrinthitis, meningeal infection will be foreseen, perhaps more frequently by the use of cisternal puncture than by lumbar puncture. Negative results of the examination are without value. Cytologic and bacterial examinations are of some prognostic value. If there are more than two to three cells per cell of Nageotte, the fluid is abnormal. If the examination for bacteria gives positive results, the prognosis is grave. In otitic infections, the Streptococcus mucosus or pneumococcus III are the most virulent and often lead to fatal complications. Patients with staphylococcic meningitis sometimes recover.

Serous meningitis corresponds to no clinical entity; it is a syndrome, characterized by meningeal signs, hypersecretion and hypertension of the cerebrospinal fluid, which is aseptic, papillary stasis, etc. This syndrome may also be due to tumor, reflex excitations or toxic irritation.

Otitic meningitis is classified as: diffuse, localized, associated and the meningeal reaction. There is one criterion for diffuse menengitis: it is always fatal. The signs of localized meningitis vary according to its location. Certain cases are curable. Gradenigo's syndrome represents a meningitis localized at the point of the petrous pyramid; ventricular hydrops (hypertensive ventriculitis of Sicard) is the result of localization that blocks drainage from the ventricles. Associated meningitis is localized around an abscess, thrombophlebitis or diffuse encephalitis. The criterion of meningeal reaction is its favorable termination. Every case of diffuse meningitis in which recovery occurs is only a meningeal reaction. The meningeal reaction is frequent in children, and is benign if the ear is promptly drained. The fluid is usually sterile, but the presence of pus is not, a priori, a fatal sign, as it may be directly infected from the focus of origin. Hautant showed that in such meningitides with septic spinal fluid and favorable outcome the patients never show signs of paralysis.

Preventive treatment consists in the radical exenteration of the mastoid process in chronic otitis. A labyrinthitis that lasts more than eight days, with increasing lymphocytosis in the spinal fluid, requires drainage of the labyrinth.

Every meningeal reaction demands intervention: removal of the auricular focus, drainage of the subarachnoid spaces and antibacterial remedies. The observations at operation will determine the procedure: mastoidectomy, sinus opening, evacuation of extradural or brain abscesses, and drainage of the labyrinth if the meningitis follows a labyrinthitis. In cases of hypertensive meningeal reaction without localizing signs, repeated lumbar and cisternal punctures suffice, but large quantities of fluid must be withdrawn. If localizing signs are present, temporal or suboccipital decompression must be added if the hypertension persists. If signs of localization and hypertension still persist, the encysted fluid should be removed, the point of election being revealed by the localizing signs. Ventricular puncture is indicated in hydrops of the ventricle. In diffuse purulent meningitis, the gravity

of the case warrants the successive carrying out, in the minimum of time, of all measures for draining the subarachnoid space: spinal punctures, two or three times daily, drainage of the pontocerebellar lake, translabyrinthine drainage and ventricular and spinal punctures. But, when recovery occurs in a case of septic meningeal reaction, spinal drainage suffices in most cases.

DENNIS, Colorado Springs, Colo.

STUDIES OF EXOPHTHALMIC GOITER AND THE INVOLUNTARY NERVOUS SYSTEM. HAROLD THOMAS HYMAN and LEO KESSEL, J. A. M. A. **96**:2014 (June 13) 1931.

Hyman and Kessel classify patients afflicted with disturbances of the thyroid gland or of the involuntary nervous system in three groups: (1) those with morphologic changes in the thyroid gland (simple goiter) but without sympathomimetic symptoms (autonomic imbalance) or elevation of the basal metabolic rate; (2) those with sympathomimetic symptoms (autonomic imbalance) but without elevation of the basal metabolic rate and with or without goiter; (3) those with autonomic imbalance goiter and definite and sustained elevation of the basal metabolic rate (exophthalmic goiter, the Graves syndrome and Basedow's disease). All patients with simple goiter, cysts or adenomas of the thyroid gland should receive iodides. The drug may be administered as the saturated solution of sodium iodide in doses of from 0.2 to 0.5 cc. daily. The salt can be added to soup or any other liquid vehicle. It should be given daily, except on Sunday, for from two to four weeks before a second examination is made. Patients with "goiterophobia" should also be given bromides or other sedatives. The patient with uncomplicated simple goiter should receive reassurance that he is no more a candidate for exophthalmic goiter than his nongoitrous neighbor, that pressure symptoms are infrequent, that the goiter is benign and that complications are rare. Within the month the gland should be reexamined. This provides ample time for the complete conversion of the hyperplasia into the colloidal stage. Whether or not the goiter responds, maintenance doses of iodide two days in the week are continued for at least a year, with the object of preventing secondary hyperplasia. Double doses are employed during pregnancy and menses. Prophylactic dosage to female children of the family is also prescribed. The promiscuous and uncontrolled use of iodized foods is inadvisable. Iodide therapy, both curative and prophylactic, should be controlled medically. In simple goiter there are four medical indications for operative intervention: (*a*) suspicion of malignancy; (*b*) objective signs in the trachea or larynx indicating pressure; (*c*) frequent thyroid apoplexy from intracapsular rupture of a brittle and thickened vessel, and (*d*) marked deformity from an unsightly goiter. The clinical management of patients with autonomic imbalance is exceedingly difficult and frequently disappointing. Whether or not the imbalance is accompanied by goiter, iodides may be exhibited and at times seem to exert as specific an effect as in true exophthalmic goiter. Ergotamine tartrate specifically depresses the thoracolumbar system and doses of from 0.001 to 0.004 Gm. three times daily may be tried. Rarely have the authors obtained a noteworthy or clearly defined clinical result. The use of endocrine products is also disappointing. Foci of infection should be eradicated. Excellent results may be obtained through psychotherapy, though no particular technic is required to study or treat these patients. A careful inquiry into the patient's routine, his ambitions and frustrations will yield a treasure trove of information. Fatigue is a common exciting factor. Therapy consists primarily in pointing out the relationship between symptoms and the psychic trauma and reassurance that the symptoms are not evidences of any organic disease or even harbingers thereof. The obvious psychic trauma is eliminated, if possible. Otherwise, the patient is advised to accept his burden and bear his cross. A word to relatives, friends or business associates is frequently helpful. Relaxation and rest are prescribed. Bromides and hypnotics are very useful symptomatically. Spending Sunday or the week-end

in bed frequently stabilizes the nervous system. A vacation may be followed by complete relief of symptoms, but in all instances patients must be warned that recurrence of the "reaction picture" will follow provocation. When the budget permits, a complete rest cure of the Weir Mitchell type may be rewarded by a gratifying result. In a few instances, the psychic trauma is not readily revealed, and more elaborate psychiatric methods, particularly psychoanalysis, are indicated. The patient with exophthalmic goiter should be institutionalized and a careful physical examination and investigation of the psychic status made. High calory feeding, sedatives and hydrotherapy are prescribed. Foci of infection are sought for and, if possible, eradicated as soon as the general condition of the patient permits. A very intimate transference between the patient and the physician is attempted. In difficult or obscure psychic conditions, the aid of a trained psychiatrist is sought, but the need is rare. Sodium iodide is immediately administered as a saturated solution from 0.2 to 0.5 cc. three times a day. Although some patients continue to present symptoms or even grow worse while in the uphill phase of the disease, the iodides are not responsible for the persistence or exacerbations of the symptoms. There are no contraindications for their use. In approximately 50 per cent of instances, more often in the younger than in the older group, striking, almost specific, improvement will occur. The morphology of the gland (adenoma) in no way modifies the response. When the effect of the iodide has reached its fastigium, surgical intervention is indicated in the following groups: (1) patients over the age of 35; (2) in the presence of pressure symptoms corroborated by roentgen or laryngoscopic observations; (3) when the gland suggests a malignant degeneration; (4) all patients with organic damage, as indicated by persistent hypertension, cardiac irregularity, alterations in the functioning of the liver or in the pigmentation of the skin; (5) two or more exacerbations of the disease, despite adequate conservative treatment; (6) all patients, young or old, who must necessarily be returned to a life of social or economic stress, or who are unable perfectly to adjust themselves to their problem, and (7) when the goiter is unsightly and regarded by the patient as a symbol of the disease.

EDITOR'S ABSTRACT.

THE ETIOLOGY OF POSTVACCINIAL ENCEPHALOMYELITIS. RICHARD THOMPSON, Arch. Path. **12**:601 (Oct.) 1931.

The occurrence in recent years of a serious acute disease of the central nervous system complicating the oldest and as yet most effective of the procedures for immunization has attracted widespread concern. Although general attention was first called to the possibility that such a complication occurs by the report of Lucksch in 1924, it was apparently first recognized in 1922 in England when four patients with an acute fatal nervous condition and a history of recent vaccination were admitted to the London Hospital. The essential lesions, as found at autopsy, were those of an acute diffuse nonpurulent encephalomyelitis. Further inquiry revealed seven similar cases in the London area. Turnbull and McIntosh, in 1926, reported these cases with full pathologic observations, and included reexamination in a similar case that had occurred in 1912. During the summer, 1923, fifty-one other cases were reported in various districts throughout England, and in November of that year the Andrewes committee was appointed by the minister of health to investigate the condition.

Since the recognition of the condition in Europe, a number of cases of nervous complications following vaccination have been reported in this country; some of these clinically and pathologically conform to the typical European cases. In most instances the onset of symptoms was rapid and the course of the disease acute. The predominant symptoms were of cerebral rather than spinal origin, and included fever, headache, vomiting, strabismus and varying degrees of clouding of consciousness. When paralysis of the limbs occurred, it was generally of the upper motor neuron type.

The typical condition can be differentiated clinically from epidemic encephalitis by the presence of a positive Babinski sign, the lack of residual lesions or recessions and, in most cases, by the absence of involvement of the muscles of the eyes. From poliomyelitis, it is differentiated by the gradual onset of the paralysis, when it occurs, and by the usually complete recovery. The majority of cases (65 per cent) had their onset between the tenth and thirteenth days, and 82 per cent between the seventh and fourteenth days. The earliest day after vaccination on which an onset occurred was the second day.

Closely related to the lack of a directly proportional relationship between the cases of postvaccinial encephalitis and vaccinations is the so-called "group arrangement" of cases, which has been noticed in many outbreaks of the disease. The English committees noticed that while many cases of the disease were isolated and sporadic, there was a tendency for the groups of cases to occur closely associated in time and place, but with no evidence of a spread of infection, since the cases occurred almost simultaneously. Grouping of cases of postvaccinal encephalitis in the same household or family has occurred, but comparatively rarely. The English committee reported two such instances, in each of which members of the family were vaccinated on the same day and showed symptoms on the same day. Two instances of more than one case occurring in the same family, but with two and three years intervening, are on record, suggesting a peculiar familial susceptibility.

That the pathologic picture presented by the postvaccinal cases of encephalitis is constant and typical, and can be definitely differentiated from those of poliomyelitis and epidemic encephalitis, is accepted by most investigators. Turnbull gave a complete résumé of his own observations and those of McIntosh, and correlated them with the descriptions of Bastiaanse (1925), Perdrau (1928), Schurman (1928) and Lucksch (1927). The distribution of the lesions is typical and constant. Focal changes occur throughout the central nervous system from cortex to lumbosacral cord. Both the white and gray matter are extensively involved. The meninges are only slightly affected, the characteristic changes occurring within the central nervous system. The essential lesions are perivascular and marginal zones of demyelinization and perivascular infiltration, largely extra-adventitial. The demyelinization is almost always around veins, and extends for long distances along their branches; it is usually complete, only a fraction of the axis cylinders surviving in any zone. In the acute cases a great number of proliferated glia cells are usually contained in the wide-meshed net of glia fibrils in the zones of demyelinization. Proliferated glia cells extend a variable distance beyond the zones of demyelinization and cause a diffuse infiltration in the most severely affected regions. Hemorrhages are rare, and, when they occur, are small and perivascular. Tigrolysis in the nerve cells is constant but complete necrosis is rare, and neuronophagia is seldom, if ever, seen.

The three most important etiologic theories, briefly summarized, are: There is much evidence in favor of the assumption that postvaccinal encephalitis is caused by the direct action of vaccine virus on the brain; two important objections to this are not yet satisfactorily explained, the lack of vaccine virus in the brain in most cases and the differences between the lesions in man and those produced experimentally in animals. The work of McIntosh may, with further corroboration, remove the second obstacle. The epidemiologic facts apparently opposed to this theory can be explained by the assumption of variations in susceptibility to the encephalitogenic action of the vaccine virus. The theory of an activation of some unknown virus is largely supported as an alternative explanation by those who regard the obstacles to the acceptance of the first explanation as unsurmountable. There is little, if any, positive evidence in favor of this theory which cannot be equally well explained on the basis of the theory that the vaccine virus is the cause. The conception of an allergic reaction as an explanation has no direct evidence in its favor.

WINKELMAN, Philadelphia.

THE RESPONSE OF A SINGLE END ORGAN. BRYAN H. C. MATTHEWS, J. Physiol. **71**:64 (Jan.) 1931.

This paper describes a series of experiments that have been made to investigate the general properties of the sensory end-organ that is stimulated by the stretching of a muscle, and is especially concerned with the phenomena of adaptation, i. e., the gradual fall in the frequency of the discharge under a constant stimulus.

The end-organs chosen for the present investigation were muscle proprioceptors, as their responses could be evoked repeatedly without difficulty, and their stimulus, stretching, could be easily measured, controlled and graded. The oscillograph was used to record the action currents from the nerves; with this instrument frequencies as high as 2,000 per second can be detected and measured. The preparation consisted of the small muscle on the upper outer side of the middle toe of the frog (M. ext. be. prof. dig. III); the contraction of this muscle causes extension of the toe with some flexion to the side. The nerve involved is the lateral branch of the peroneal. Some 500 preparations were made. The muscles from the preparations were usually stained and examined at the conclusion of an experiment. It was usually possible to find one end-organ of the type described by Cajal and classed as a muscle spindle; once, two were found, but never more. There seems little doubt that the structure that responds to stretch and tension is the muscle spindle. In all preparations examined it was found about the middle of the muscle.

The method used is described and illustrated. The paper is divided into three parts. The first records results of loading, its regularity, its constancy, the relation of load to discharge, the resting discharge, the rate of loading, extension and tension, the refractory period and the recovery curve of the nerve ending, all illustrated by graphs. The second part concerns the factors affecting the response to stimulation, such as temperature, ionic composition of the surrounding fluid, grouped impulses, an electric current, hydrogen ion concentration and hydrocyanic acid. Part 3 has to do with the mechanism of adaptation.

Matthews makes the following observations: If the muscle is kept in a small quantity of Ringer's solution for some time, the response in the nerve is first depressed and then disappears, but returns to its initial magnitude when the Ringer's solution is changed. The frequency of response is roughly proportional to the logarithm of the load. When the muscle is loaded rapidly, the interval between the impulses set up is only a little greater than the absolute refractory period of the nerve fibers concerned, and also the time relations of the action currents of these impulses are modified, showing that they are traveling in an incompletely recovered nerve fiber. It seems possible that these rapid discharges may be due to continuous rather than intermittent excitation of the nerve fiber. The viscosities of the end-organ may account for the discontinuities in the response when small loads are applied rapidly. The interval between the impulses at the highest frequency recorded varies with temperature in much the same way as does the absolute refractory period of a nerve trunk. The behavior of the end-organ is greatly modified by the ionic composition of the surrounding fluid. In sodium chloride the frequency of discharge remains high for some minutes; addition of either calcium or potassium alone reduces the response below that obtained in Ringer's solution. Moreover, calcium and potassium appear to have an antagonistic effect. Rhythmic discharge of grouped impulses occurs when the preparation is kept at 25 C. in sodium chloride. The response can be modified by passing a steady electric current through the muscle. The change in the response depends on the direction of current flow. Hydrocyanic acid is found to cause a transient increase in the response, later followed by extinction of the discharge.

Adaptation was examined, and it was found that there is an after-effect lasting several seconds after the stimulus is removed. This adaptation remainder was measured quantitatively, and it was found to develop as stimulation was prolonged and to vanish in a few seconds after the stimulus was removed. The

adaptation remainder was found to be a function of the total stimulation, i. e., the magnitude of the load and the time during which it has been acting.

The author suggests the following hypothesis to account for the observed behavior of these end-organs: It is probably safe to assume that the recovery depends on the gradual restoration of some component, e. g., a replenishing of the store of ions that maintain the surface polarization. It seems possible to account for most, if not all, of the facts on the assumption that the rate of recovery depends on the concentration of this substance adjacent to the surface membrane, that the concentration is reduced by the stimulus and whenever an impulse is set up, and that it is restored from two sources: (*a*) by diffusion from adjacent regions and (*b*) by a process of replacement, probably involving a chemical breakdown.

ALPERS, Philadelphia.

SPONDYLITIS DEFORMANS. CHARLES W. BUCKLEY, Brit. M. J. **1**:1108 (June 27) 1931.

This paper is based on a clinical and radiologic study of 150 cases of spondylitis of various types. Cases in which there were no obvious changes on roentgen examination were excluded, as well as cases of osteitis deformans. Two main groups are differentiated: spondylitis ankylopoietica, which includes both the Bechterew and the Marie-Strümpell types, and spondylitis osteo-arthritica, the degenerative or hypertrophic form. The latter group is sometimes designated as "laborer's spine." To these may be added traumatic, tuberculous and possibly syphilitic spondylitis.

Of the 60 cases of the spondylitis ankylopoietica type, 6 were in women. In this group, infection seems to be the most important etiologic factor. The incidence of a gonorrheal infection was rather high. A history of injury was present in a considerable number. The most striking feature was osteoporosis of the vertebral bodies and often of the ilia and sacrum; this is considered by the author as the primary change, preceding any alteration in the ligaments. Deformity and curvature depend in great part on the posture adopted by the patient in an attempt to secure comfort. Pain in the back is a frequent early symptom, while pain in the distribution of one or both sciatic nerves is due to pressure on the nerve roots as they pass through the spinal foramina. Ossification and ankylosis characterize the pathologic process. Inflammation of the joints between the articular processes arises early and leads to marked tenderness of the spine on pressure or percussion. Ossification of the capsules of these joints, of the ligamenta subflava and of the interspinous ligaments quickly follows, and the spine becomes rigid. Ossification of the anterior common ligament is not a conspicuous feature in man, but it is so in horses. The articular processes become firmly ossified, and the bodies are joined together by ossified disks and ligaments, and the spine becomes a rigid bar. The costovertebral joints may be implicated early, and intercostal pain is a common symptom. Lipping of the anterior edges of the bodies often occurs, with increasing deformity. Exostoses do not occur. This is an important diagnostic sign. The sacro-iliac joints become completely ankylosed early in the disease, if ankylosis begins in the lower part of the spine. The hip joints quickly follow suit. Pain and stiffness may be present in the knees and shoulders, but in the author's series ankylosis was not present. The progress of the disease varies greatly. The onset may be acute and the progress rapid, while in other cases it may be just the reverse.

Spondylitis osteo-arthritica has also been described as spondylosis deformans to indicate its degenerative character, but the ankylopoietic form is productive of greater deformity. There were 61 patients of this type in the series, of whom only 2 were women. Over half of the cases occurred in patients between 50 and 60 years of age. The most important factor in its production appears to be the wear and tear and strain of heavy labor. Thirty-one of the patients were coal miners. The author believes that roentgen examination of any group of men

over 50 engaged in similar laborious work would show evidence of spondylitis osteo-arthritica in probably 50 per cent.

The onset in this disease may be sudden, although roentgen examination will reveal that the pathologic process has been of long duration. Stiffness of the back is the prominent symptom, though pain may occur, owing to pressure on the nerve trunks from exostoses. It is not a seriously crippling disease, and the degree of flexibility of the spine may be remarkable. The primary change is probably in the intervertebral disks, which undergo degeneration or partial atrophy. Exostoses are then thrown out to support the weakened articulation. The author thinks that, in addition to the strain, there is probably some additional factor, toxic or infective, necessary to produce the more extreme examples. Syphilis, he thinks, is probably one of the most important of such influences.

Healed or quiescent tuberculosis of the vertebrae may present an appearance resembling the osteo-arthritic form. Kümmell's disease, or spondylitis traumatica, may simulate the first variety. Malignant disease may also give rise to difficulties in diagnosis.

The essential point in treatment is to recognize the infectious feature of the ankylopoietic form and to take steps to prevent the development of kyphosis, ankylosis of the hips, etc., and to pay special attention to the defective calcium metabolism by correcting vitamin deficiency and other disorders of nutrition.

FERGUSON, Niagara Falls, N. Y.

ASSIMILATION OF ATLAS AND COMPRESSION OF MEDULLA: THE CLINICAL SIGNIFICANCE AND PATHOLOGY OF TORTICOLLIS AND LOCALIZED CHRONIC ARTHRITIS DEFORMANS OF THE SPINE. ISTVÁN BÉZI, Arch. Path. **12**:333 (Sept.) 1931.

The upper part of the bone-walled channel that contains the medulla is solid. The lower part, on the contrary, is formed by separate bones — the atlas and the axis — and their articulations. As a consequence of the anatomic conditions, the channel may be narrowed, especially by upward or backward positional changes of the odontoid process of the second cervical vertebra, which forms part of the frontal wall. Under normal circumstances these changes in the position of the odontoid process occur only by movement of the atlanto-occipital articulation. This movement, however, is extremely slight, as shown by the investigations of Virchow. The movement is restricted by the resistance of the strong, tense ligaments around the articulations. Together with the special ligaments of the odontoid process itself, they assure the normal fixation of the odontoid process.

There are many pathologic changes that may alter the relation between the odontoid process and the medulla. This communication deals only with changes in the bone wall of the channel, principally with the bones themselves and their articulations, although the latter are of less importance. These pathologic changes may be total or partial destruction of the bones or interruption of their continuity. The occipital bone that forms the base of the skull, the atlas and the axis may be altered separately. However, several members of this triad may undergo pathologic changes at the same time, and the articulations frequently participate in the process.

Among the pathologic changes of bones that may cause compression of the medulla, dislocation of the odontoid process of the axis seems to be the most important. Observations show that this dislocation is mostly caused by partial destruction of the bones around the medulla due to inflammation or to trauma.

According to the author's observation, the odontoid process may become "dislocated" in consequence of an assimilation of the atlas, and may cause compression of the medulla. But it seems that the assimilation must reach a certain degree, while the mass of the atlas remains underdeveloped. This assimilation of the atlas causes pathologic changes similar to those in arthritis chronica deformans, owing to the abnormal mechanical-static conditions. This, therefore, supports the functional theory of the etiology of arthritis chronica deformans. The patho-

logic function has to be regarded as secondary, i. e., as a consequence of the primary constitutional factor — the malformation of the atlas.

As to the compression of the medulla, the alterations of the articulations described are of great importance. By their successive development the volume of the bone-walled channel around the medulla is changed accordingly, and in this way a vicious circle arises between compression and the conditions in the joint.

On the basis of this case, and according to the cases published, a lethal compression of the medulla may occur when the odontoid process is dislocated at least from 7 to 10 mm. backward, and from 18 to 25 mm. upward. In considering compression, the development of hydrocephalus and hydromyelocele is of great importance.

As the atlas may be more or less melted together with the os occipitale after various inflammatory processes, the author proposes that the term "assimilation" be reserved for congenital cases, i. e., those based on malformation. The adhesions of the bones arising in extra-uterine life (in most cases with inflammatory origin) should be called "synostosis."

Synostosis alone may become a hindrance to puncture of the cisterna. It is probable that in the case of assimilation, in which, as a rule, the posterior arch of the atlas is absent to a greater or less extent, puncture of the cisterna is easier.

WINKELMAN, Philadelphia.

IS POLIOMYELITIS A DISEASE OF THE LYMPHATIC SYSTEM? MONTROSE T. BURROWS, Arch. Int. Med. **48**:33 (July) 1931.

If the work of Burrows on infantile paralysis is to be accepted, it will be necessary completely to revise our concept of this illness. He believes that the lymphatic system is the primary center of the disease, lymphatic hyperplasia the fundamental lesion, and the Peyer's patch the most common focus. His contention is that the condition occurs repeatedly without being diagnosed, and that the occasional case with a neurologic complication is so conspicuous as to be considered characteristic. He quotes Parkes and Neal, who say that 75 per cent of patients with poliomyelitis never show involvement of the central nervous system, and insists that even this figure is too low. Since most of the experimental work has been done by making inoculations directly into the central nervous system of monkeys, research data are necessarily biased in favor of neurologic complications.

Burrow's conclusions are based on more than fifty autopsies that he performed during the epidemic of 1916. In all cases he found a general lymphoid hyperplasia, which was most marked in the Peyer's patches. When present, the tonsils were always involved. The lymph glands were edematous, and there was active proliferation of lymphoid cells—the picture being that of a true hyperplasia. Primary involvement of nerve tissue was not found. In the subarachnoid spaces there was active proliferation of endothelial lining cells, followed by congestion and edema; glia-cell proliferation occurred only in severe and long-standing cases. The perivascular spaces in the nervous system were also distended. In one third of the cases the dentate nucleus of the cerebellum was affected in this manner. Secondary changes occurred in the dorsal root ganglia, but not in the nerve trunks.

The portal of entry seems to be the intestinal lymphatic apparatus. From there the condition spreads to lymphatics of other parts, and in unusual cases, in which resistance is low, the lymphatic spaces of the spinal cord are involved, producing the picture commonly called poliomyelitis and mistakenly considered the essence of the disease. This is substantiated by the clinical observation that the disease begins as a gastro-intestinal upset.

To quarantine patients with severe cases in which there is involvement of the spinal cord and to allow a hundred times as many patients who have the disease in milder form to go at large is useless in discouraging epidemics. Burrows hopes that a method of vaccination or inoculation can be worked out to prevent the disease, just as smallpox and diphtheria are now prevented. Since a mild case

produces no harmful results, and one attack confers immunity, the parallel, epidemiologically, between poliomyelitis and smallpox seems logical. The fact that the disease occurs more commonly in children is the result of the immunity that most adults have received owing to mild, unnoticed attacks in childhood. Transmission is probably by direct contact, and the germs may be harbored in the mouths of apparently healthy persons. The incubation period is from three to seven days.

Poliomyelitis, as Burrows pictures it, is the rather unusual end-result of a generalized lymphatic disease, which begins in the follicles of the intestine. In most cases, mild but vague intestinal symptoms occur, followed by recovery and immunity. In less resistant patients, wider extension occurs and other lymphatic structures are involved; here, too, recovery, immunity and freedom from neurologic complications is the rule. In a small percentage of cases, resistance is so low that the nervous system is invaded, and the syndrome commonly recognized as infantile paralysis occurs. The paper is illustrated by photomicrographs of lymphatic, vascular and nervous tissues showing the changes described.

DAVIDSON, Newark, N. J.

THE ACTION OF DRUGS ON THE VASCULAR AND MUSCULAR FACTORS CONTROLLING THE INTRA-OCULAR PRESSURE. J. COLE, P. M. DUKE-ELDER and W. S. DUKE-ELDER, J. Physiol. **71**:1 (Jan.) 1931.

Duke-Elder has previously advocated the theory that the intra-ocular fluid is a dialysate of the capillary blood. In one of his former papers it was seen that the intra-ocular pressure is maintained at its normal level by the balance between the hydrostatic pressure in the capillaries and the difference between the osmotic pressures of the aqueous humor and the capillary plasma; and, if the theory of dialyzation is correct, all the variations in intra-ocular pressure should be accounted for by the physical forces involved in such a process without the intervention of anything in the form of secretory energy. The present work is an attempt to review the mechanism and amplify the results. The instruments employed and the technic followed are outlined in detail.

From observations based on the variations in intra-ocular pressure in intact animals and in the artificially perfused eye, from temperature records taken in the anterior chamber, from the direct observation of the vessels of the iris and from records of the muscles, the authors reach the following conclusions with regard to the action of drugs on the eye uncomplicated by general systemic effects: Epinephrine in small doses dilates the capillaries, increasing their permeability and raising the intra-ocular pressure; in large doses it constricts the vessels, lowering the intra-ocular pressure; in any dose it stimulates the plain muscle of the orbit, raising the intra-ocular pressure, and dilates the pupil, which is without effect on the intra-ocular pressure. Solution of pituitary contricts the arterioles, lowering the intra-ocular pressure, and stimulates the plain muscle of the orbit, raising the intra-ocular pressure. Histamine (in the dog and cat) dilates the minute vessels and increases their permeability, raising the intra-ocular pressure, provided the vessels have sufficient tone; otherwise its action is confined to a constriction of the arterioles, an action that lowers the intra-ocular pressure. Choline dilates the minute vessels and stimulates the voluntary striped muscles of the orbit, raising the intra-ocular pressure. Nicotine manifests its action entirely by stimulating the plain and striped muscles of the orbit to contract, thus raising the intra-ocular pressure. Atropine dilates the minute vessels and increases their permeability, thus raising the intra-ocular pressure, and relaxes the plain muscle of the orbit, thus raising the intra-ocular pressure. Physostigmine dilates the small vessels and increases their permeability and also increases the tone of the voluntary muscles of the orbit, thus increasing the intra-ocular pressure. Curare lowers the intra-ocular pressure by relaxing the tone of the voluntary muscle.

So far as the present investigations go, there is no evidence of any secretory activity influencing the intra-ocular pressure; all the changes in the latter are compatible with the theory that the aqueous humor is a dialysate. The pulse beat, the respiratory excursion and the extra-ocular muscles exert a sufficient influence on the intra-ocular pressure to maintain an efficient pressure circulation of the aqueous humor.

ALPERS, Philadelphia.

A RAPID AND PERMANENT METHOD FOR STAINING MYELIN SHEATHS. CYRIL COURVILLE and ARAM KRAJIAN, Arch. Path. **11**:920 (June) 1931.

Method.—Hardening: For rapid diagnosis with fresh tissue, boil the blocks for one minute in 10 per cent formaldehyde and then leave in the same solution in a paraffin oven for five minutes before cutting frozen sections. When the section is not demanded in a short time, fix the tissues in 10 per cent formaldehyde for twenty-four hours or longer. Sections: Cut frozen sections 10 microns thick, and place in a large dish containing tap water. Mounting: Draw the sections onto slides and let the excess water drain off for about a minute; dehydrate with absolute alcohol, pouring on a few drops two or three times, each time allowing it to evaporate. Blot and dip the slide in a thin celloidin solution, fixing the section to the slide. Dip the slide in tap water for a few seconds. Mordanting: Cover the section with 15 per cent hot aqueous solution of ferric chloride for five minutes. Drain the solution from the slide. Do not wash. Staining: Cover the section for five minutes with equal parts of hematoxylin solution and distilled water, heated to 60 C. This stains the section extremely black. Washing: Wash thoroughly in tap water. Destaining: Remove the excess stain in a 1 per cent aqueous solution of ferric chloride, dipping the slide in and out of the solution until the gray matter begins to appear in contrast to the dark medullary substance. This takes place in from ten to twenty-five seconds. Washing: Wash the slide quickly in tap water. Differentiation: Cover the section with a 0.25 per cent aqueous solution of potassium permanganate and shake with the fingers to secure even differentiation, which takes place in about five seconds. This step should be controlled under the microscope. Washing: Thoroughly wash the section in tap water. Dehydration: Remove water from the section after draining off the excess by pouring on a few drops of absolute alcohol and draining off, repeating three or four times. Blot between filter paper. Clearing: Plunge the section in a container of equal parts of aniline oil and xylene for about three minutes and then in xylene for another three minutes. Mounting: Mount in Canada balsam or gum damar.

Results.—The interpretation of the results is the same as with the Pal-Weigert method. The myelin sheath stands out as a ringlike structure surrounding the unstained axis cylinder core in cross-section. In longitudinal section, it appears as a light-bluish strand, observed characteristically in the gray matter of the cord and the deeper layers of the cerebral cortex. The accompanying illustrations show the details emphasized by the method. In rapid degenerations the myelin is seen to be broken up into globules in the course of the nerve fibers. If the process is a slower one, as in tabes dorsalis, the typical shrinking and distortion of the fibers may be seen.

The method seems to be best adapted to frozen sections, for the authors have had poor results with paraffin sections of formaldehyde-fixed material. No results were obtained with tissues fixed in Zenker's fluid.

WINKELMAN, Philadelphia.

THE SYNDROME OF THE NASAL NERVE. CARLOS CHARLIN, Ann. d'ocul. **168**:86 (Feb.) 1931.

Neuritis of the nasal branch of the fifth nerve produces a symptom complex which, according to Charlin (The Syndrome of the Nasal Nerve, *Ann. d'ocul.* **168**:86 [Feb.] 1931), if once noted will not be forgotten. This syndrome is

characterized by extreme pain, usually disproportionate to the amount of ocular inflammation, and is accomplished by nasal difficulty and, especially, marked hydrorrhea. There is usually an associated ulcer of the cornea or iritis, but sometimes a slit-lamp is required to detect involvement of the eye. Local treatment of the eye is of little value unless associated with the use of epinephrine and cocaine in the nose. If the nasal mucous membrane supplied by the nasal branch of the fifth nerve is cocainized, the eye improves rapidly. Five cases are reported, and an interesting schematic drawing is appended. In conclusion, the author points out that the instillation of cocaine in the eye does not relieve the pain. The following differential diagnostic points between conditions of the sphenopalatine ganglion and those of the nasal nerve syndrome are made:

	Nasal Nerve	Sphenopalatine Ganglion
Anatomy:	The nasal nerve innervates the eyeball and the anterosuperior portion of the nasal fossa, the skin of the nose and the nasofrontopalpebral region	The sphenopalatine ganglion innervates the apex of the orbit, the central and posterior portion of the nasal fossa and part of the buccal cavity; no cutaneous innervation
Syndrome:		
	1. Inflammatory lesions of the eye	1. No ocular lesions
	2. Marked continuous congestion of the anterosuperior portion of the nasal fossa; marked congestion of the anterior portion of the inferior turbinate.	2. Intermittent congestion of the posterior nasal fossa; marked congestion of the posterior portion of the middle turbinate
	3. Superficial painful points; painful point on the ala of the nose	3. No superficial painful points
	4. Cutaneous eruptions on the nose and the skin of the frontopalpebral region nasally	4. No cutaneous eruption
	5. Immediate cessation of pain and improvement of the disorder of the eye by the application of cocaine and epinephrine to the mucous membrane of the nose anteriorly on the external wall	5. Immediate cessation of painful crises by the application of cocaine and epinephrine on the nasal mucous membrane in the region of Meckel's ganglion, that is, in the posterior part of the nasal cavity on the external wall

BERENS, New York.

THE RÔLE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND IN GROWTH: WITH SPECIAL REFERENCE TO THE TEETH AND MAXILLAE. WILLIAM G. DOWNS, JR., Arch. Path. **12**:37 (July) 1931.

It is apparent from a survey of literature on the endocrine glands that endocrinologists in general are of the opinion that glands of internal secretion markedly affect the growth, shape, size and placement of the teeth. With the exception of the work of such men as Erdheim, Toyofuku and Gies as regards the effect of the parathyroid gland on the teeth, these opinions are in large part based on empiric and clinical reasoning only.

There is in the anterior lobe of the hypophysis a substance that markedly affects the general growth of the organism. This effect is exercised in the direction of maintaining the water content of the tissues of the animal at a high level and in reducing the animal's tendency to put on fat. Its tendency is to increase the total mineral content of the tissues over a normal level for a given period of age. Its effects are shown in the size of the jaws. Further, there is a probable toxic effect, evidenced microscopically in the liver, kidneys and lymphogenic organs and due probably to the toxic products of too rapid stimulation of metabolic processes. There is likewise an apparent tendency for the growth-promoting hormone to stimulate especially the growth of the supporting tissue elements.

If these results are compared with those of Donaldson and others on the normal growth of rodents, the conclusion seems warranted that the effect of the extract

of the anterior lobe of the hypophysis is to stimulate these animals in the early period of rapid growth (the third phase of Donaldson) to an even greater rate of growth and to prolong this period somewhat into the latter, or fourth, phase. It also seems apparent that these effects are in no sense specific for the dental mechanism or inclined to be productive of specific anomalies of the teeth, but are exercised simply in the direction of rate and time of development, and that if there is a specific effect involved, it is in the direction of further accelerating the formation of connective tissue, which is already being formed at a rapid rate at this period, and of increasing the fluid content of these tissues.

It seems apparent from these and earlier studies that the eruption and growth of the teeth and of their investing tissues may be considered only as a part of the general phenomena of growth of the body, and may be influenced by the pituitary gland in a specific direction only insofar as the time and velocity of development of the various tissues and organs may be influenced.

WINKELMAN, Philadelphia.

INVESTIGATION ON MICROGLIA AND OLIGODENDROGLIA: IV. VITAL STAINING. D. BOLSI, Riv. di pat. nerv. **37**:13 (Jan.) 1931.

In order to elucidate the debated question of the nature of microglial elements, and because of the attempts made by some authors to consider microglia as a part of the reticulo-endothelial system, the author has undertaken a series of experiments with the vital staining of nerve tissue. He recalls the experiments of Tester, Cavallaro, Gozzano, Bellavitis, Corria and Russell, most of whom concluded that the microglial element takes the vital stain as do the elements of the reticulo-endothelial system. De Robertis denied, however, that the microglia takes the vital stain in any way different from other glia cells. The author's investigations uphold the belief that under normal conditions microglial elements do not store vital stains, and that the storage takes place only under pathologic conditions when direct lesions are made in the nerve tissue. It also brings out that with the use of acid stains, and as trypan blue, the only element of the glial series that stores granules of the stain is the microglial element. According to the author, only when the vital stain is prolonged for an unusually long time, fifteen or twenty days by means of hypodermic injections, is the stain found also in other elements, as for instance, the astrocytes, or even the nerve cells. The author has succeeded in counterstaining the cellular elements containing the stain particles with his own modification of the Hortega stain, thus confirming the microglial nature of the trypan blue-containing elements.

Of interest is the fact that in the compound granular corpuscles the stain is not detectable, which might be explained on the basis of Dogliotti's observation that cells containing a large amount of fat do not stain vitally, and that it is only after the fat has been absorbed that the vital stain is detectable in these cells. The fact that it is only in pathologic conditions that the microglia takes the vital stain may be explained on the basis of biologic changes occurring in the elements while undertaking a reactive function. At the same time, the difference in behavior between the microglia and elements of the reticulo-endothelial system may point to the somewhat different nature of the microglia from the two elements of the reticulo-endothelial system. The microglia might be an element more identical with histiocytes and not necessarily with the reticulo-endothelial system, unless one is willing to admit that all histiocytes belong to the reticulo-endothelial system, which would require, according to some investigators, a relationship of the cells with the endothelium and a closer connection of the element with reticular fibrils.

FERRARO, New York.

TREATMENT OF MANIC-DEPRESSIVE PSYCHOSIS: SURVEY OF LITERATURE. L. E. HINSIE and S. E. KATZ, Am. J. Psychiat. **11**:131 (July) 1931.

To indicate the trends of thought in the history of the treatment of the affective psychoses, the authors review the literature of therapy in this form of mental

disease. A classified bibliography of almost six hundred references is given. Reviewed historically, it is seen that the aim of therapy has advanced from treatment of the symptoms to treatment of the patient, from attention to the actively psychotic periods only to care of the patient as a unified personality even during lucid intervals. The authors also consider the question of prophylaxis, pointing out the importance of maintaining psychotic wards in general hospitals. They view with approval the establishment of small psychopathic hospitals for intensive study of acute and treatable cases. The change in the public attitude toward mental disease is also emphasized as evidence of progress.

Among the therapeutic measures, the authors list: (1) restraint, (2) psychotherapy, (3) pharmacotherapy, (4) endocrine treatment, (5) physiotherapy, (6) physical and surgical measures, (7) pyrotherapy, (8) occupational therapy and (9) intelligent nursing care. Restraint they condemn as short-sighted, superficial and ineffective. Psychotherapy is largely limited to psychoanalytic methods, and most of the papers on the subject are favorable toward this technic. Drugs are used chiefly for sedative effects, and are generally approved only for emergency use. If prolonged narcosis could be achieved it would be valuable, but no adequate method for inducing extended sleep has been found generally acceptable. Of endocrinotherapy and treatment by surgical means, including removal of foci of infection, the literature, on the whole, seems skeptical, in spite of the enthusiasm of the advocates of these methods. Of the various physiotherapeutic measures, hydrotherapy has been most highly praised. Pyrotherapy by malarial inoculation or injections of foreign protein has met with little success in the treatment of manic-depressive psychoses. Occupational therapy has proved its value, though some authors emphasize the need for caution in prescribing work. Hinsie and Katz conclude with emphasis on the importance of intelligent nursing care during the active stage of the psychosis and the value of social service assistance after the patient has left the hospital.

DAVIDSON, Newark, N. J.

BITEMPORAL PARACENTRAL SCOTOMA. CHARLES E. G. SHANNON, Arch. Ophth. **6**:544 (Oct.) 1931.

This case of bitemporal paracentral scotoma presented two interesting features: the form of the scotoma unassociated with disease of the pituitary body, and an unusual etiology. The patient complained of blurred vision and severe pain in the eyes, the syndrome having occurred a few days after immunizing injections of vaccine had been given. A diagnosis of glaucoma was made at that time. The present report is given after a lapse of two years though made shortly after the case was first seen by the author. The right eyeground showed perivasculitis, the macula being dark and somewhat granular, and, just above the macula toward the temporal side, two small yellowish patches of exudate about the size of a blood vessel, with clearcut and well definited margins. These were not present in the left eye. The blind spots were not enlarged. Both eyes showed a small paracentral scotoma, just temporal to the point of fixation. During the next four months, the fields, taken at varying intervals, showed no change. The Wassermann and Kahn reactions of the blood were negative. The sinuses were normal. Two abscessed teeth were extracted.

A roentgen examination of the head revealed that: the bones of the skull were of average normal thickness and had normal vessel markings; there was a little thickening of the bone along all the suture lines, a not unusual but not exactly normal observation, indicating possibly some imbalance in calcium metabolism (there was a fairly large calcareous deposit in the region of the pineal gland); the sella turcica was smaller than the average; there was some sclerosis around the left mastoid; the accessory sinuses were clear; there was possibly slight cloudiness of the right sphenoids. The spinal fluid was normal.

The patient was seen in consultation by de Schweinitz, who suggested the possibility of minute vascular lesions in the chiasm, usually of syphilitic origin. There were no signs suggestive of syphilis in this case, however. The patient

had received injections of serums against typhoid, dysentery and cholera, all having been given on the same day. It seems logical, then, that the original diagnosis in this case was correct—minute but permanent vascular lesions in the chiasm, of toxic origin, arising from injections of serum.

SPAETH, Philadelphia.

POTENTIAL CHANGES IN THE ISOLATED BRAIN STEM OF THE GOLDFISH. E. D. ADRIAN and F. J. J. BUYTENDIJK, J. Physiol. **71**:121 (Feb.) 1931.

The present experiments fall into line with earlier work in showing changes that can be localized and related to the normal activity of the brain. The preparation employed was the isolated brain stem of the goldfish, removed from the skull and placed on a glass slide, thus avoiding all extraneous electric changes. The brain stem on its glass slide was placed on a stand carrying two nonpolarizable electrodes (silver, silver chloride) ending in moist threads. The recording system was a valve amplifier leading to a Matthews oscillograph and a loud speaker. Photographic records illustrate the results.

It was found that rhythmic potential waves may be recorded from the brain stem under study. The waves are of long duration (up to one-fourth second) and recur at intervals that vary from about one to three seconds. The respiratory movements have about the same range of frequency, and the potential waves presumably coincide with the activity of the respiratory center. Each wave is caused by the vagal lobes developing a negative potential with respect to other parts of the brain stem. The change is usually monophasic and of smooth contour, but small oscillations are occasionally present. Potential waves of various form may occur in the midbrain. Some of these are of smooth contour, but often there are rapid oscillations (from 10 to twenty a second) superimposed on a much slower change. The oscillations resemble those obtained from a nerve trunk when a number of fibers are discharging rhythmically and more or less in unison. The slow potential waves may be due to nerve fiber discharges, but their form makes it more probable that they represent a slow change in the nerve cells or dendrites.

It is pointed out that if the nerve cells become depolarized when they are excited a slow development and decline of the excitatory state would be accompanied by potential waves of the type described, and the axon discharge would rise and decline in frequency. The rhythmic activity of the respiratory center in the goldfish can occur in the entire absence of sensory impulses.

ALPERS, Philadelphia.

A STATISTICAL STUDY OF DELUSIONS IN THE MANIC-DEPRESSIVE PSYCHOSES. KARL M. BOWMAN and ALICE F. RAYMOND, Am. J. Psychiat. **11**:111 (July) 1931.

The types of delusions found in patients admitted to the Boston Psychopathic Hospital between 1923 and 1927, for whom a diagnosis of dementia paralytica, schizophrenia or manic-depressive psychosis was made were correlated with data as to sex, diagnosis, marital condition, personality and several other factors. Forty-two per cent of manic-depressive patients had no delusions; the same percentage applied to patients with dementia paralytica; of schizophrenic patients, on the other hand, only 10 per cent were free from delusive ideas. The commonest delusion in the affective and schizophrenic classifications was a persecutory one, accounting for 20 per cent of the manic-depressive patients and almost 60 per cent of those with dementia praecox. Among patients with dementia paralytica, grandiose delusions were somewhat more numerous than persecutory ideas (27 and 20 per cent, respectively). The authors then correlated the distribution of delusions with various personal data. In each case they estimated the number of patients of a certain type who would be expected to show delusions of a specified char-

acter. These estimates were then compared with the actual incidence. It was found that married women showed more persecutory delusions than would be expected, and single women showed fewer. In the affective psychoses there was a greater delusion-free group in both sexes among patients of superior intelligence than was statistically expected. A close correlation between hallucinations and persecutory delusions was noted in all classifications except in schizophrenic women. No constant correlations were found between the delusional types, on the one hand, and such factors as age, nativity, religion, personality, somatic status, white cell count of the blood or previous attacks. With regard to alcoholic habits it was found that more abstinent patients with schizophrenia and dementia paralytica were free from delusions than was expected.

DAVIDSON, Newark, N. J.

ATLANTO-OCCIPITAL PUNCTURE: COMPARATIVE VALUE OF CISTERNAL AND LUMBAR PUNCTURE. G. AMADUCCI, Riv. di pat. nerv. **37**:70 (Jan.) 1931.

The author reports on the comparative conditions of the cisternal and lumbar fluids. The technic that he uses consists in drawing a horizontal line between the extremities of the two mastoids and a perpendicular line originating in the occipital protuberance and following the medial line along the spinal process of the cervical vertebrae. The point of junction of these two lines is the point of election for the introduction of the needle. The patient is therefore put in a lateral position, with the head at the same level as the body and slightly bent forward. The needle is then introduced with a slight direction upward; the medial position of the needle should be strictly maintained, as lateral deviation might involve some lateral spinal or cerebellar arteries.

As a conclusion of his investigations, the author differs from Riser and Sorel so far as pressure is concerned, because in his estimation the value of the pressure of the lumbar fluid is somewhat higher than that of the cisternal fluid. In his manometric investigations the author used only a single manometer, the Claude manometer, and did not follow the Ayer method of the simultaneous application of two manometers. The albumin and cellular values (lymphocytes) of the cisternal and spinal fluids harmonize with those reported by Riser, Laborde, Weigeldt, Ayer and Salomon, who found figures somewhat higher in the lumbar fluid. In eight of eighteen cases, following cisternal puncture, the author reports also some increase in temperature from a minimum of 38 C. (100,4 F.) to a maximum of 40.2 C. (104.3 F.) in a period of from five to twelve hours after the withdrawal of the fluid. The author interprets the febrile reaction as an expression of a functional disequilibrium of the centers located in the tuber cinereum following the vasodilatation resulting from the transitory depression in the subarachnoid fluid.

FERRARO, New York.

"GENUINE EPILEPSY": MICROSCOPIC CHANGES IN THE CAPILLARY SYSTEM AS PROBABLE ETIOLOGIC FACTOR. D. M. OLKON, J. Nerv. & Ment. Dis. **72**:538 (Nov.) 1930.

The author studied microscopic vascular changes in the brain, internal viscera and skin in dogs, and in babies obtained at cesarean section. Many observers have seen a relationship between convulsions and vascular changes. Preliminary work was done on more than 300 normal persons from 1 to 40 years of age, who never showed the slightest sign of convulsion. A second group comprised subjects with convulsions of a "genuine epileptic type." Capillary distortion was especially marked in the young epileptic persons, but none could be found in those at any age without some distortion. Studies of the capillary patterns of 17 babies obtained at cesarean section showed no capillary changes, while in the cutaneous capillaries of children born with distocia and forceps delivery distortions were common. Eighteen healthy dogs anesthetized with 40 per cent chlorbutanol, injected intraperitoneally, hyperexcitability in this way being eliminated as far as possible, were

subjected to craniotomy, and the vessels of the pia and brain examined under the microscope. Strychnine and histamine were used as exciting agents in the production of the convulsive state. Immediately following the convulsion a disorganization in the subpapillary plexuses, with all sorts of distortion, spasm and kinking, was observed. Blood cells remained imprisoned and immobile in the large atonic capillaries of the pia-arachnoid. The small capillaries showed the maximum destruction. The author thinks it is probable that brain trauma from birth resulting in capillary hemorrhage gives rise to metabolic imbalance in susceptible persons, and that "genuine epilepsy" is in the vast majority of cases due to exogenic rather than endogenic influence.

HART, Greenwich, Conn.

THE HISTOPATHOLOGY OF POSTENCEPHALITIC DISEASES. S. KÖRNYEY, Arch. f. Psychiat. **92**:372, 1930.

Környey discusses the pathology of postencephalitic conditions on the basis of six cases observed during the disease and in which postmortem examinations were made. He finds that a marked loss of cells always occurs in the substantia nigra, especially of the pigmented cells. In some cases there are also an involvement of the pallidum and rarely of the striatum. In all of the cases there was also a diffuse increase in the glial network, along with glial scars.

The changes in the substantia nigra affect the ectodermal as well as the mesodermal elements and present certain system characteristics. By this is meant that they affect only fibers and elements that belong to this system, and not those that merely pass through it. The author is also of the opinion that the progressive nature of the lesion in this region does not necessarily mean that there is a continued activity of the virus. He thinks that the process is of a degenerative nature, being caused by the injury during the acute process, which has decreased the vitality of the cells.

He further stresses the point of differentiation between the clinical and pathologic pictures of genuine parkinsonism and that caused by encephalitis. In the genuine form, clinically there is a characteristic rigor, and anatomically the controlling feature is a disease of the pallidum. In the postencephalitic form, clinically there is akinesia or bradykinesia and anatomically mainly an effect on the substantia nigra.

MALAMUD, Iowa City, Iowa.

HAVE PSYCHOPATHOLOGICAL CONCEPTS A PRACTICAL VALUE IN NEUROPSYCHIATRY? EDWARD A. STRECKER, Ment. Hyg. **15**:456 (July) 1931.

There are many methods of managing neuroses — rest, hydrotherapy, removal of foci of infection, endocrine treatment and others; but it is an understanding of the disturbed mental mechanisms that offers the most fruitful field for bringing relief. No such understanding is possible without some grasp of a few fundamental psychopathologic concepts that form, as it were, the alphabet of psychotherapy. First of these is the complex — the group of ideas held together by a strong emotional bond, craving conscious expression. Denied a conscious outlet, the complex expresses itself in distorted forms, represented often by neurotic symptoms. The psychotherapist's first aim is the discovery of the nature of these complexes. Many unfortunate complexes owe their origin to unpleasant incidents. In the effort to forget or repress the disagreeable happening, the patient retains its emotional associations, which can be stirred into disquieting activity every time he comes into contact with anything that might symbolize the original unpleasant incident. To prevent this, the patient must be taught to consider the affair as objectively as possible, to accept the situation, to profit by the lesson — in a word to rid the incident of as much affective influence as possible. To this process Strecker applies the happy term "emotional desensitization." He closes with the perhaps too optimistic thought that if the person can be brought to a frank realization of the nature of his conflicts, it will be impossible for him to retain his neurotic symptoms.

DAVIDSON, Newark, N. J.

EPIDEMIC MENINGITIS MINOR. J. V. C. BRAITHWAITE and W. MITCHELL INNES, Brit. M. J. **2**:567 (Sept. 26) 1931.

This report is based on a study of thirteen cases of meningitis observed from Feb. 21 to April 8, 1931. The epidemic nature of the disease is suggested by the fact that no cases were seen either prior to or following the dates mentioned. Eight of the cases were associated with bronchopneumonia of a mild type; the other five were apparently primary. The onset was sudden in seven and insidious in six. Typical symptoms of meningitis were present. All except one of the patients recovered. In the fatal case, death was apparently due to a combination of diphtheria and bronchopneumonia. The primary cases cleared up very shortly after lumbar puncture, usually within twenty-four hours. In the secondary cases, the meningeal signs cleared up on lumbar puncture, while the bronchopneumonia ran a short course. No other treatment for the meningitis was attempted.

All of the patients were young children, and ten of them were boys. During the time of their occurrence there were two mild epidemics prevalent; cerebrospinal meningitis and influenza. The authors believe, however, that the very frequent coincident bronchopneumonia points rather to an influenzal infection being the cause, and they remark, that it does not appear unreasonable to suppose that this form of meningitis may result from mild infections of various natures, influenza perhaps being the commonest; and they suggest that the name "meningitis minor" be applied to them to differentiate them from the infinitely graver suppurative or tuberculous forms.

FERGUSON, Niagara Falls, N. Y.

THE PHENOMENA OF MÉNIÈRE'S DISEASE. F. H. QUIX, Nederl. tijdschr. v. geneesk. **75**:366 (Jan. 24) 1931.

In the case described by the author, Ménière's disease began with tinnitus in the left ear followed after a year by vertigo and vomiting. The otologist at the time could discover only a slight labyrinthine dysfunction and nystagmus that was less prominent with the left ear than the right. Several years of improvement followed. Four years later, the seizures recommenced more violently. The vestibular reflexes on the left side were more difficult to elicit than those on the right. After a time these objective differences disappeared, the seizures of vomiting and vertigo ceased, and the only residue was a diminution in hearing on the left side. It is noteworthy that in Ménière's disease the patient may remain free from symptoms of disease during the free intervals, so the otologist is obliged to discover the signs through labyrinthine stimulation and tests for hearing at the time of the attacks. Hence the great difference in the objective signs during the attack as contrasted with the free intervals. Nystagmus and vasomotor and secretory processes in other parts of the body disappear rapidly. The disturbance of hearing, mostly of labyrinthine character, can change, be absent or disappear. Signs of labyrinthine irritation and paralysis which manifest themselves through nystagmus, caloric reaction, past pointing and galvanic excitability also fluctuate in the same manner.

HART, Greenwich, Conn.

RECENT LEGISLATION IN ENGLAND AND WALES AFFECTING THE CARE AND TREATMENT OF MENTAL PATIENTS. J. R. LORD, Ment. Hyg. **15**:512 (July) 1931.

Legislation affecting persons with mental disease has usually been concerned with their protection or custody; the recent Mental Treatment Act marks the first recognition by Parliament that mental disease is primarily a matter of medical concern. The voluntary admission of patients to institutions is provided for, with the added safeguard that a patient so admitted shall not be retained more than a month if he becomes incapable of expressing his will on the subject; the friends and relatives of patients are permitted to live as boarders in the hospital. Provision is also made for the reception of patients as "temporary" guests in a

hospital for mental diseases, for a stay of less than six months. The Board of Control has been reorganized so as to consist of a woman, a lawyer and two physicians. Perhaps the most significant feature of the new law is the severance of mental disease from pauperism, by the provision that tax-aided mental patients are not to be deemed as being in receipt of poor relief. The changing attitude toward those mentally ill is reflected by the new terminology used; it is provided that: asylums be called "mental hospitals," patients, "boarders," and that the expression "pauper lunatic" be replaced by "rate-aided person"; even the word "lunatic" is barred, the phrase, "person of unsound mind" being substituted.

DAVIDSON, Newark, N. J.

RESULTS OF SYMPATHETIC GANGLIONECTOMY AND RAMISECTOMY FOR CHRONIC ARTHRITIS. JAMES R. MOORE, J. A. M. A. **97**:172 (July 18) 1931.

The author records some personal experiences in the onset, progress and treatment of arthritis, especially the reaction which he, as a physician, has experienced in the newer surgical methods of treatment; e. g., a quadrilateral sympathetic ganglionectomy and ramisectomy. He summarizes his experiences thus: A case of arthritis developed without antecedent illness in himself, aged 36, when he had resided for many years previously in a warm, dry climate. The case became progressively worse in spite of the elimination of possible foci of infection combined with the usual and recognized methods of treatment, pursued over a period of three years. Marked improvement both subjectively and objectively and at least an apparent arrest of the progress of the disease were observed in both the upper and lower extremities following a quadrilateral sympathetic ganglionectomy and ramisectomy. Improvement in general health and mental attitude followed closely on relief of the local joint condition. The author would not hesitate to recommend to any one suffering from arthritis the radical surgical procedures referred to, provided a fair trial had been given other recognized modes of treatment and the signs in the case were such as would indicate in the light of past experience that a favorable result might reasonably be expected.

UNILATERAL OPTIC ATROPHY IN CRANIAL INJURIES IN THE FRONTAL REGION. L. GENET, Ann. d'ocul. **168**:213 (March) 1931.

Genet observes that frontal injuries are increasing in frequency, owing, in his judgment, to the increased use of motorcycles and automobiles, which apparently are conducive to injuries in the frontal and orbital regions. He has recently seen several frontal injuries, and points out the importance of roentgenographic study of the optic canal. This often permits one to diagnose a fracture in the region of the optic canal. If ophthalmoscopic signs are not found in the first few days, the absence of the direct pupillary light reflex with preservation of the consensual reflex is an important observation. He states that optic atrophy is usually first noted on about the tenth day and requires two or three months before it is fully developed. The optic atrophy is not necessarily complete, and the central vessels remain almost normal. In regard to pathogenesis, he points out that anatomists have shown that the optic nerve is adherent to the optic canal above, and that fracture of the optic canal will lacerate the optic nerve. In addition to this, pathologists have demonstrated that small hemorrhages in the optic nerve sheath are usually found in these cases. The author believes that the hemorrhages are due to lacerations which produce the optic nerve atrophy.

BERENS, New York.

INVESTIGATION ON MICROGLIA AND OLIGODENDROGLIA: III. DEGENERATIVE CHANGES. D. BOLSI, Riv. di pat. nerv. **37**:1 (Jan) 1931.

The author has studied the degenerative changes of microglia, especially the so-called acute swelling. Acute swelling has already been described by Ferraro and Morrison, Meduna, Gozzano, Vizioli and contrasts with the assertion of

Penfield and Cone that the microglial elements do not undergo acute swelling, which is characteristic for the oligodendroglia. The author has studied the action of arsenic, mercury and lead on rabbits, and confirms the existence of acute swelling of the microglia cells in the brain. He points out, however, that the microglia is more resistant than the oligodendroglia to such a process. In some chronic intoxications the author has been able to find a combination of hypertrophic reaction and acute swelling of the microglia. Such a combination, though with predominance of hypertrophy, is found in chronic meningo-encephalitic processes.

Though both microglia and oligodendroglia undergo the same type of degenerative changes labeled as acute swelling, it does not necessarily follow that microglia and oligodendroglia have identity of function. According to the author, the two elements, though having a different origin and function, may undergo the same type of degenerative changes.

FERRARO, New York.

ARTERIOSCLEROTIC DISEASE OF THE OPTIC NERVE. BERNARD J. ALPERS and I. J. WOLMAN, Arch. Ophth. **6**:21 (July) 1931.

In this article, the authors discuss arteriosclerotic disease of the optic nerve with either a partial destruction or a complete atrophy of the optic nerve. Examples of both forms were seen and are discussed. The article is based on the report of the case of a woman, aged 44, with essential hypertension, cardiac enlargement, slight aortic insufficiency and some ocular symptoms. The necropsy showed compression of the optic nerves, especially the left, by the sclerosed internal carotid arteries and with focal changes in the optic nerves and the chiasm.

The pathogenesis of arteriosclerotic visual disturbances as connected with the optic nerve is not always the same. It is not essentially a direct pressure atrophy —a true secondary atrophy of the optic nerve. There are some cases in which arteriosclerosis of the small vessels within the optic nerves itself plays fully as important a rôle. The first is a true secondary partial nerve atrophy. The second is a lack of nourishment within the tissues, with the resulting changes described, namely, a focal loss of nerve tissue with perivascular gliosis.

SPAETH, Philadelphia.

PROFESSOR FREUD'S SEVENTY-FIFTH BIRTHDAY. WILLIAM A. WHITE, Ment. Hyg. **15**:527 (July) 1931.

Even Freud's bitterest opponents cannot deny the tremendous effect he has had on modern thought, especially on clinical psychology. White compares Freud to Copernicus and Darwin. Each made a signal advance, one in astronomy, one in biology and one in psychology. The world was different after the work of each had been done than it was before, and the difference was due to this work. Each wounded man's ego; each was ridiculed and hated. In each case, the dislodgment of man from his position of petty self-aggrandizement widened the horizons of his knowledge and placed him in an even more inspiring position. The starry universe and the material body seem to White to be more comprehensible than the human mind; to have contributed something to an understanding of this mysterious and elusive entity is to have performed a work of epochal significance. White concludes by quoting Havelock Ellis: "When any great person has stood alone against the world, it has always been the world that lost."

(This article was an address delivered May 6, 1931, at a dinner in honor of Dr. Freud's seventy-fifth birthday.)

DAVIDSON, Newark, N. J.

THE INDUCTION OF TETANY IN RACHITIC RATS BY MEANS OF A NORMAL DIET. ALFRED F. HESS, MILDRED WEINSTOCK, H. R. BENJAMIN and J. GROSS, J. Biol. Chem. **90**:737, 1931.

Tetany can be induced in rachitic rats simply by an abrupt change from a rickets-producing ration, high in calcium and low in phosphorus, to a normal ration

of dried milk, or of dried milk and whole wheat. The fall in calcium in the serum that is brought about by this means develops within forty-eight hours, but is maintained only a few days. This striking reaction is not due to an absolute or a relative increase of phosphorus in the dietary, but to a sudden shift in the calcium : phosphorus ratio in the subsequent diet as compared to the preliminary diet. When this ratio, calcium : phosphorus, is decreased from about 4 : 1 to 1 or 1.5 : 1 tetany ensues, whereas if it is decreased only to about 2 : 1 the fall in calcium and nervous symptoms do not occur. Attention should be directed to the effect of marked alterations in the constitution of dietaries, as such shifts may help to explain nutritional disturbances that are inexplicable merely from the standpoint of adequacy.

FREMONT-SMITH, Boston.

THE CASE FOR AND AGAINST THE OPERATIVE TREATMENT OF ANGINA PECTORIS. WALLACE M. YATER and ARTHUR P. TREWHELLA, Am. J. M. Sc. **182**:35 (July) 1931.

This study was stimulated by the ill effects of cervical sympathectomy in a single case of angina pectoris. In 138 cases of neurectomy, 40.5 per cent of the patients had complete relief; there was an operative mortality of only a 6.5 per cent, irrespective of the type of operation performed. Thirty-one per cent of the patients who survived were made less comfortable because of pains in the side of the face, jaw or neck and paresthesias of variable duration. Against the operative treatment are also cited the efficacy of amyl nitrite or nitroglycerin and the apparent absence of influence on the course of the disease. White's method is considered the most efficient one to date. The anatomic and physiologic features of the innervation of the heart and aorta are summarized and found to be incompletely known.

MICHAELS, Detroit.

PARALYSIS OF THE ABDUCENS NERVE ACCOMPANYING A CASE OF MASTOIDITIS: AN UNUSUAL FORM OF GRADENIGO'S SYNDROME. E. MARTIN FREUND, Arch. Otolaryng. **13**:717 (May) 1931.

Gradenigo's syndrome is: paralysis of the external rectus muscle, unilateral pains in the temporoparietal region on the same side and otitis media on the same side. The diplopia usually appears before operation, but at times it is postoperative. A case of Gradenigo's syndrome is reported with an unusual complication: transitory ptosis and edema of the upper eyelid on the opposite side, controlled by a transfusion of blood. The anatomy of the abducens nerve is discussed, and the types of this syndrome are classified: (1) cases with simple mastoiditis which progress favorably; (2) cases with further basal involvement, such as the facial, optic or vestibular, and (3) cases with septic meningitis.

HUNTER, Philadelphia.

RIGID PROGRESSIVE SYNDROME WITH SPASM OF FORWARD TORSION. LUDO VAN BOGAERT and PAUL INGELBRECHT, J. de neurol. et de psychiat. **31**:118 (Feb.) 1931.

The authors report the case of a girl, aged 11, in whom dystonia with spasm of forward torsion had been developing for five years. This was followed by the development of difficulties in swallowing and later by a "progressive rigid syndrome," with generalization of voluntary motor activities and the association of athetoid movements and megasynkinesis. There was later found a weakness of downward gaze. These symptoms are suggestive of a condition described by Madame Vogt as "status marmoratus," a case of which has been previously described by the authors. The authors do not believe that the condition could be explained on the basis of epidemic encephalitis.

WAGGONER, Ann Arbor, Mich.

MONGOLISM IN ONE OF TWINS. J. I. WARING, Am. J. Dis. Child. **41**:351 (Feb.) 1931.

As further evidence of the view that mongolism is due to a defect in the individual germ plasm and not to general physical enfeeblement in the parents, Waring presents a case of this form of feeblemindedness in one of dizygotic twins. These twins were the offspring, born at full term, of a mother, aged 35, and a father, aged 45. They were fed in infancy on dried milk formulas; they had had measles and influenza at the same age. Waring describes them at the age of 4½ years; the boy seemed normal, with a bright expression and a slender build. The girl was a typical mongolian, showing retarded growth, slanting eyes, large furrowed tongue, lax joints, cold pale skin, a square head and square hands. The Wassermann reaction was negative in both children.

CEREBRAL TRAUMA AND ITS RELATION TO MENTAL DEFICIENCY. N. W. WINKELMAN, Am. J. Psychiat. **10**:611 (Jan.) 1931.

There is a large group of patients, Winkelman believes, in whom mental deterioration results from cerebral trauma. These mental changes are the result of mechanical pressure brought about by the aseptic meningitis induced by the pouring of the blood into the subarachnoid space; this causes a fibroblastic proliferation which blocks the drainage of spinal fluid by way of the arachnoid villi. As a result, fluid accumulates and a hydraulic cast is formed, causing atrophy of the underlying cortical tissue. The plan of dehydration that Winkelman has found so serviceable in epilepsy is offered as a means of improving the mental condition of the infants and adults who show this posttraumatic mental defiiciency.

ACROMEGALY WITH DIABETES MELLITUS AND XANTHOMA DIABETICORUM. ELAINE P. RALLI, Arch. Int. Med. **47**:329 (Feb.) 1931.

Ralli reports a case of acromegaly with severe diabetes mellitus and xanthoma diabeticorum. The acromegaly preceded the onset of the diabetes. All the characteristic symptoms of diabetes were present, including typical sugar tolerance curves and a pronounced hypercholesterolemia. The dermal lesions were most prominent when the cholesterol level reached its peak, which was 5,900 mg.; under active diabetic treatment they diminished considerably in size and number. The features of acromegaly were marked, including the characteristic changes in the bony structures and an increase in the size of the sella turcica. The increased activity of the pituitary gland made this case more refractory to treatment with insulin.

DAVIDSON, Newark, N. J.

Society Transactions

GERMAN NEUROLOGICAL SOCIETY

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O. FOERSTER, M.D., *President*

DEUTSCHE ZEITSCHRIFT FÜR NERVENHEILKUNDE **115**:147, 1930; **116**:2, 1930

DR. W. J. BERNIS, Rochester, N. Y. *Abstractor*

(Concluded from p. 480)

RESTITUTION. DR. O. FOERSTER, Breslau.

In diseases of the nervous system recovery may take place in three ways: (1) by reversion of the noxa, although it has brought about a change in the structure of the nervous system, but has left no definite destruction; (2) through regeneration of destroyed nerve tissue, and (3) through reorganization in irreparably destroyed nerve substance and conducting tracts, that is, by a change in the operation of this remaining part of the large working association which all parts of the nervous system form. This reorganization is often designated as compensatory. Foerster does not discuss reversion by noxa.

I. *Restitution of Motility.*—1. Restitution in Lesions of Spinomuscular Conducting Tracts: (*a*) Regeneration. In interruption of the conduction of peripheral nerves, regeneration is often possible, up to complete normal restoration. It depends mainly on the new growth of neurofibrils from the central part of the peripheral section up to the organ of reaction. The deefferented muscle, completely severed from its union with the nervous system, becomes reneurotized. When reneurotization takes place through the same nerve that formerly supplied the muscle, Foerster speaks of it as "Homoreneurotisation." Under favorable conditions, regeneration may be spontaneous. Often it is accomplished only through the operative removal of the hindrance that is in the way of the growing fibrils. By means of nerve suture and neurolysis, the fibrils growing out from the central part of the peripheral nerve make the way free and enter the peripheral part, and thus reach the functioning organ.

The point must be made that nerve suture requires years of electric treatment and exercise. Complete recovery can take place under such treatment by competent persons. Bad results are due to failure to observe this rule. It often happens, when the electric treatment is stopped, that a setback takes place, that even the returned faradic irritability is again lost and returns only after months of renewed treatment.

The succession of restitution corresponds to the distance that the growing fibrils have to close up to the organ of function. In sutures high up it generally requires a much longer time for the beginning of restitution and the complete recovery of function of all the muscles supplied by the sutured nerve. The proximal muscles recover more quickly than the distal ones. In plexus sutures, the deltoid, pectoralis major, biceps and triceps recover more quickly than the distal muscles.

The time for recovery fluctuates from case to case. In some, restitution begins after from two to four weeks. In some, complete recovery takes place in five or six weeks or in two or three months. These are considered quick recoveries.

Many reported examples of quick recovery do not stand the proof. Yet some patients recover quickly. Foerster found in many of his rapidly recovering patients, in whom a long interval had elapsed between the trauma of a severed nerve and the operative procedure (a year or longer), and in whom there was a considerable separation from the central stump, that after operative intervention the excitability of the paralyzed muscles returned and they contracted strongly. The peripheral nerve section had therefore contained nerve fibers. Foerster is not inclined to assume that these nerve fibers have worked themselves through a thick connective tissue capsule into the distal portion of the nerve. He rather assumes that in such cases an autoregeneration of neurofibrils took place within the distal portion of the nerve, in the sense of Bethe and Spielmeyer, and that this was responsible for the rapid recovery; that after suture, the outgrowing fibrils from the central stump of the nerve thrust themselves onto the previously outgrown fibrils in the distal portion, and consolidation took place. In such cases it was also noticed that the recovery of function took place simultaneously in all muscles supplied by the nerve, unlike what is observed in successive restitution. In regeneration, the peripheral portion of the sectioned nerve is surely, in the first place, the line of growth for the newly growing fibrils; it also offers the material for this in slowly protracted processes. But the Schwann cells of the peripheral nerve portion, under certain conditions and only in exceptional cases, appear themselves to be capable of forming neurofibrils, true to their origin from cells in the medullary tube, which later have something in common with the ganglion cells and the nerve fibers.

Regarding the biologic recognition of regeneration, in the first place, it is recognized by the return of function and by contraction of the muscles under voluntary innervation impulses. But great care is necessary in determining whether a movement brought about by voluntary action is the result of contractions of former totally deefferented muscles. The involuntary reactions are more important in questions of regeneration, and in the first place are to be considered changes in electric irritability. With galvanic stimulation more prompt contraction is brought about; it loses its wormlike character, and later again becomes lightning-like. The chronaxia, which has been delayed to 100 or over, gradually diminishes and reaches normal.

It is unquestionable that in regeneration the reestablishment of function depends on the renuerotization of the formerly deefferented muscles. The restitution of function is highly complicated; it represents a wonderful phenomenon. The neurofibrils of the central portion of the nerve grow to an overproduction, and they not only grow in a straight line in the cable of the peripheral portion, but diverge with many crossings and entwine in many directions. Each central cable becomes connected with all the cables of the distal portion. In this way there are brought about entirely different connections between the individual anterior horn ganglion cells of the nerve and the individual muscles supplied by it as compared with what was formerly the case. A median suture offers an example. To select only the spinal nuclei of three of the muscles supplied by the median nerve, the pronator teres, the flexor sublimis and the opponens pollicis, normally each of the nuclei is connected with its muscle by a large number of nerve fibers. In regeneration only a part of the newly growing neurites of the pronator nucleus reach into the pronator; a second part finds its way into the flexor sublimis, and a third part reaches into the opponens. Likewise only a part of the nerve fibers growing out from the flexor sublimis nucleus again reach the flexor sublimis; other fibers reach into the pronator and into the opponens. The same is true for the opponens nucleus. The pronator, the flexor sublimis and the opponens, therefore, are now largely coordinated with different anterior horn cells than before. A part of the former pronator nucleus has become now the flexor sublimis nucleus; another part the opponens nucleus.

In voluntary movements the spinal nuclei of the muscles partaking in the movement receive their innervation from the cortex from the particular area that more or less is the focal representation of the individual muscles. The fact that

notwithstanding the complete rearrangement of the connection between the anterior horn cells of the cord and the individual muscles brought about as a result of regeneration, the sutured nerves and readjusted muscles can yet be innervated presupposes that there was also a complete rearrangement between the corticospinal connections. When voluntary pronation is now performed, the cortical elements that are in connection with the anterior horn cells of the spinal pronator, which now sends its neurites to the flexor sublimis, are no longer brought into activity; it must be brought about through another course, and cortical elements must be brought into action that are in connection with the ganglion cells of the spinal flexor sublimis nucleus or opponens nucleus. It is possible that corticospinal tracts are made use of now that existed long before, but were until now inappropriate for pronation. This readjustment can thus be simply formulated. The function of the former spinal pronator nucleus, within the nuclei of the sixth and seventh cervical segments, has been taken over by a large number of ganglion cells belonging to many other nuclear columns and lying within the segments from the sixth cervical up to the first dorsal. Likewise, in place of the original cortical pronator focus, which is composed of more or less closely lying motor cortical elements, a large number of elements belonging to various other foci and widely scattered over the motor cortical zone form a new association which finally functions as well as the preexisting one.

Mention is made of the method of "bridging over" which becomes necessary when nerve suture is not possible on account of too great diastasis between the stumps. The one useful method is the so-called autoplastic procedure, that is, the interplantation of pieces of nerves from the patient between the central and the peripheral portions. For this purpose cutaneous nerves are used. The fibrils from the central portion can grow through the interplanted nerve, which, of course, becomes degenerated, and thus enter the peripheral portion. But the result of nerve bridging is less favorable than that of nerve suture.

As regards the question of the so-called free outgrowth of the nerve fibers from the central nerve stump to the organs of function: For practical purposes it is only to be considered when the free central end of the nerve is implanted directly into the reneurotized muscle. The sprouting fibrils grow out into the muscle and reform new end-plates.

The deefferented muscle can also be reneurotized with nerves from other parts. This method Foerster designates as heteroreneurotization. Different technics have been recommended. The best results are obtained when the freshly sectioned healthy neurotisator is sutured with circular sutures to the peripheral portion of the sectioned paralyzed neurotisand (copulation method). It can also be accomplished by suturing the peripheral portion of the neurotisand in one of the notches of the neurotisator (inoculation method).

It is understandable that the return of function in heteroreneurotized muscles depends also on a profound reorganization, on a complete rearrangement of the corticospinomuscular connections. This can be observed especially in such cases. In facial paralysis, when the central accessorius is sutured to the peripheral portion of the facial nerve and the fibers of the former have grown into the facial musculature, the former accessorius nucleus has become a facial nucleus. When the shoulder is raised voluntarily, the face also contracts at first. The former accessorius nucleus is not yet freed from its original corticospinal connections. In this state the facial musculature is incapable of voluntary innervation; this must come in a roundabout way through the voluntary raising of the shoulder. But this is soon changed; the face can again be voluntarily innervated. However, the movement of the face is always accompanied by an involuntary raising of the shoulder. In this state of restitution, therefore, there is a connection between those cortical stimuli complexes underlying the representation of facial motility and the motor cortical focus for raising the shoulder, but the shoulder raising focus still acts in its own capacity; all muscles engaged in raising the shoulder are innervated. But finally the associated shoulder movements in voluntary innervation of the face are discontinued. A dissociation must have taken place within the cortical focus

of the shoulder raisers, separating the accessorius nucleus into those innervating the shoulder and those for the motility of the face. It is also possible that unused tracts running from the cortical facial focus to the accessorius nucleus are now being made use of.

A regeneration of the anterior roots of the cord is also possible. Foerster reports a successful operation that he performed in a case of severe injury to the cauda at the third lumbar vertebra. Restitution began first one year after the operation, and it took three and one-half years to effect complete recovery.

(*b*) Reorganization. It is remarkable how, in cases of partial or complete deefferentation the organism summons all available forces that may assist in bringing the muscle to a normal function. When the deefferentation is not complete, available peripheral nerve tracts are largely made use of, due to the not infrequent presence of abnormal motor nerve branches. Here can be mentioned the results obtained by anastomosis between large nerve stems by means of the so-called double innervation of certain muscles. It is to be recalled that most muscles are multiradicularly and multisegmentally innervated.

When a muscle is not completely deefferented, the increase in the innervation power of the remaining motor nerve fibers is shown in the action current of the muscle by the increase in the number and height of the amplitude of the individual current strokes.

Of the many forces that partake in the replacement of function in cases of total deefferentation of a muscle, Foerster discusses only two kinds. One is the making use of the physical properties of the completely deefferented muscle itself. The muscle replaces its motion, although with not too great a force, but with one which in muscles extending over several joints suffices to bring about a movement in the distal part when the proximal part is actively moved. In complete deefferentation of all flexors of the fingers following total sectioning of the median and the ulnar nerves, when the hand is voluntarily and energetically outstretched, thus stretching the long finger flexors, the fingers may then be strongly flexed.

Another property of a deefferented muscle that is capable of producing in loco a motor effect is its elasticity, the power of again contracting after it is stretched and the stretching power ceases. In complete paralysis of the triceps, a stretching of the forearm can be brought about when the arm is first voluntarily bent and the innervation of the flexors is suddenly stopped. Then through the bending the elasticity of the triceps comes into play and effects the outstretching of the forearm. The motility of completely deefferented muscles brought about by mere elasticity may be so effective that the novice may not suspect the muscle to be deefferented, or if the case is one of nerve suture it may appear as if the muscle was again reneurotized.

Another type of movement is the so-called pendulum and hurling movement. In a case of complete paralysis of all the scapulohumeral muscles of the joint, the patient is sometimes able to hurl the upper part of the arm up to a vertical position by going through a number of thrusting forward and backward movements of the shoulder girdle, by which the upper part of the arm is set into motion like a pendulum. By adjusting each thrust so that the pendulum increases in amplitude, the patient finally succeeds in bringing the arm to a vertical position. Other pendulum movements can be observed in paralysis of the hips.

Other therapeutic means in deefferented muscle groups are the muscle tendon transplantations. Second to these is tenodesis, of which Perthes' operation is an example. Finally arthrodesis is to be mentioned.

2. Restitution in Interruption of the Cord: It is generally denied that regeneration takes place in interruption of the spinal cord tracts. In complete interruption of the cord, suturing has so far resulted in complete failure. Foerster, however, is of the opinion that regeneration of the tracts is possible under certain conditions. He relates a case with symptoms of complete interruption of the cord extending over many years. At operation he found a large extramedullary tumor which had compressed the cord to the thinness of paper. For a year there was

no change in the condition, but then gradual improvement began to set in. After four years, motility had returned and was as good as normal. Had death occurred at the time that the operation was performed, and had the cord been examined anatomically, the conclusion would have been drawn that, as the result of the compression, there was present a complete degeneration of the ascending and descending tracts. Yet conduction returned in this case. That it depended on regeneration is indicated by the length of time before restitution began, and by the slow and gradual progress over a period of years before complete recovery was established. Foerster is inclined to assume that a regeneration, that is, a growing out of neurites from the oral part of the cord into the caudal degenerated part, was possible, although the compression extending over years destroyed all nerve parenchyma at the place of pressure; the glia interstitial tissue, the Schwann cells and the central nerve fibers remained and retained their connection. This longitudinally arranged interstitial tissue has functioned as a tract for the growing fibrils, similar to the activity of Schwann cells and Büngner's bands in peripheral nerves.

This is not proved. But Foerster has observed several similar cases, and he thinks that the problem of regeneration of cord tracts is subject to new experimental proofs. In complete section of the cord, conditions are entirely different. Here the glia connection between the two parts of the cord is severed. Structural changes have taken place in both stumps as a result of the trauma; the oral and the caudal stumps are closed by a proliferation of mesodermal tissue. Nerves cannot grow through this hindrance.

3. Restitution in Interruption of the Pyramidal Tracts: In acute interruption of the pyramidal tract, as in after excision of the anterior central convolution, there is first of all a complete arrest of voluntary innervation of the contralateral extremities. The reflex irritability of these muscles is also more or less involved or arrested. The paralysis is at first flaccid; the tendon reflexes may be absent, hence reflexes that have been considered as pure spinal reflexes. This initial areflexia, according to Foerster, can be explained only thus: In this large cooperate activity in which all parts of the nervous system join, when such an important member as the pyramidal tract is suddenly removed, the entire common reflex activity at first becomes insolvent.

This initial areflexia does not last long. The removal of the cortical partnership from the common reflex activity is soon done away with. Not only do the reflexes return, but they are greatly increased, due, as Jackson thought, to the loss of the cortical inhibition over the spinal reflex mechanism.

Also the voluntary innervation power of the muscles returns sooner or later to a certain degree in most cases. To understand this, it must be recalled that in voluntary movements the motor innervation impulse from the cortex is transmitted to the muscles, not alone through the pyramidal tract but also through a large number of different extrapyramidal motor tracts springing from the cortex, which course through different parts of the internal capsule to the different subcortical centers (thalamus, striatum, pallidum, substantia nigra, nucleus ruber, cerebellum), and from there is transmitted to the cord and the muscles. Many cortical areas are active in bringing about a voluntary movement. Pyramidal and extrapyramidal corticosubcortical spinal muscular conducting tracts work together. When the pyramidal tract is suddenly cut off, the entire combined activity at first becomes incapable of expression; therefore, at first there is a complete inability of voluntary innervation of the muscles, regardless of the anatomic integrity of many other members of the association. But soon there follows a reorganization of the remaining members, and voluntary motility returns to a certain extent. On account of the peculiarity of the extrapyramidal cortical areas and tracts, only complex movements, especially stereotyped synergic movements, take place. The pyramidal tract is capable of innervating particular groups of muscles, individual muscles or even parts of muscles; the extrapyramidal cortical areas and the tracts coming from them bring about only innervation complexes, synergies. When the pyramidal tract is interrupted, the individual innervations are missing; the extrapyramidal stereotyped synergies appear on the scene. The bending synergies and extension synergies of the extremities are the only movements of which one

is capable when the pyramidal tracts have been removed, and which he must perform when he wishes to make another voluntary movement.

The muscles are under the control not alone of the opposite hemisphere but, to a large part also, of the hemisphere of the same side. In disturbance of one hemisphere there are still left the homolateral tracts, the homolateral pyramidal tracts, which are of service. Due to the latter the hemiplegic patient learns some innervations, to a certain extent, and is able to participate in the stereotyped extrapyramidal synergies. This remaining pyramidal tract, working together with the extrapyramidal corticosubcorticospinal tracts, may develop to considerable importance. This is especially observed in unilateral processes occurring in early childhood. Infantile hemiplegia often shows considerable restitution as a result of individual muscle group innervation; not only may there be a great modification in the stereotyped extrapyramidal synergies that form the basis of all voluntary motion, but in those cases they may perform a large variety of individual or isolated movements of the different parts of the extremities. In cortical lesions, in addition to the homolateral pyramidal tract, there is also the support from the corticocallosocapsular tract coming from the other hemisphere (Mingazzini). It is especially interesting that in cases of infantile hemiplegia the sound hemisphere may show considerable hypertrophy. However, Foerster does not think it proved that the hypertrophy represents a morphologic expression of the increased function of the homolateral pyramidal tract. Subcortical tracts have also been hypertrophied in such cases. Also in adults, through systematic exercise it is possible to develop the homolateral pyramidal tract to a great extent and thus bring about a restitution of the hemiplegia.

With the restitution there follows a change in the spinal anterior horn gray matter, which had suffered as a result of the pyramidal tract interruption. The increase in the spinal reflex activity is an essential component of the pyramidal tract syndrome, and from it, on the one hand, especially from the enormous increase of the rotating reflexes of the muscles, the so-called spasticity, there develops a great hindrance to the production of voluntary movements.

When the stretching reflex of muscles is weakened or removed by resection of the posterior roots, voluntary motility is often considerably improved. The same result can be accomplished when the tendons of the spastic muscles are plastically enlarged or when a plastic muscle is deefferented through partial resection of its motor nerves.

On the other hand, elimination of the pyramidal tract, which is no longer capable of exercising an inhibitory activity over the afferent stimuli, acts as an advantage in the performance of voluntary movements. As a result of these uninhibited afferent stimuli the spinal anterior horn gray matter is at once loaded, as it were, and the cortical impulses coming to it are more readily received. The strongly spastic muscle is usually also better capable of voluntary innervation. In spastic contractures of the extensors of the legs, voluntary innervation ability belongs to the extensors; in spastic contractures of the flexors, to the flexors. When the posterior roots are cut in a case of spastic paralysis in which some voluntary inhibitory ability still remains, it may happen that the remaining ability is entirely lost. If a few roots were left, then through these there is a gradual return of the "loading" of the anterior horn gray mass and with it a return, to some extent, of voluntary motility. The interesting fact is then observed that those muscle groups to which the reflex irritability has returned are also capable of voluntary stimulation.

There are many valuable therapeutic methods to bring about restitution in pyramidal tract syndromes. Exercise is one of them, but often the marked spasticity interferes. The spasticity can be overcome by the following methods: 1. Total tenotomy of the tendons of the spastic muscles. This must be done only on the muscles that are to be eliminated. 2. Plastic enlargement of the tendons of the spastic muscles. 3. Partial deefferentation of spastic muscles; for example, the quadriceps, or in the arm the pronator teres or the adductors. 4. Resection of the posterior roots.

4. Restitution in Cerebellar Lesions: In a case of left cerebellar tumor, Foerster removed the entire left cerebellum, including one half of the worm. This was at once followed by a complete flaccid homolateral hemiplegia with loss of the tendon reflexes. The tendon reflexes soon returned, but the extension reflexes remained absent for a long time; later they partly returned. Voluntary motility began to return after three weeks. At the same time two kinds of disturbances were noticed: a noticeable paresis, embracing all muscles of the arm and leg, and a high grade of ataxia, resembling a marked posterior root ataxia. The paresis gradually improved and disappeared entirely; the ataxia soon assumed the characteristic cerebellar symptoms of static and kinetic action tremor, so that the innervation of the agonists was not, as in the normal state, a continuous flowing one, but followed in rhythmic periods, showing the presence of a definite reciprocity between the agonist and the antagonist innervation. This, too, entirely disappeared. Eighteen months after the operation only a slight nystagmus to the left remained. At first the eyes were turned to the right and could not be turned to the left at all; this all disappeared.

The patient, a child, at first could not sit nor stand up. On sitting up, she immediately fell on her back and to the left side. This tendency to fall to the left, that is, to the side of the lesion, was also noticed when she was already able to sit and stand up. When all symptoms disappeared, there was still a slight tendency to turn to the left when the child walked with the eyes closed. In the course of time even this disappeared and now no noticeable defect is present.

5. Restitution of Coordination Disturbances in Posterior Root Interruption: Posterior root ataxia is the result of the loss of afferent stimuli, which are necessary for the gradual and timely regulation of the motor impulses. In the loss of the tactile and deep afferent manifestations in such cases visual assistance may take place. It is to be recalled that the ataxia in the tabetic patient is more pronounced when he fails to watch his gait. The optical influence is also observed in the therapeutic compensatory exercise of the tabetic patient, when visual assistance is of great help. Cutaneous characteristics may appear for the lost proprioceptive manifestations. The brain cortex itself, without the intervention of afferent assistance, may more or less adequately distribute impulses. This observation indicates that those cortical stimuli complexes which are assigned for the movement representation are capable of determining, on the part of the cortex itself, the problem of adequate distribution of impulses without the intervention of afferent characteristics.

One of the components of posterior root ataxia is the marked abnormal innervation of the agonists in voluntary movements. The flinging gait in tabes is well known. This overinnervation of the agonists definitely appears soon after sectioning of the roots as an expression of the increase in number and the increase in amplitude of the individual action current thrusts of the agonists when attempts at voluntary movements are made. Foerster observed it in two of his operative cases, one involving the arm and the other the leg. This initial overinnervation gradually adjusts itself.

II. *Restitution of Sensibility.*—1. Restitution in Interruption of Peripheral Nerves: (*a*) Regeneration. While a free outgrowth of motor nerve fibers seldom takes place without having at its disposal a degenerated portion of a nerve as a tract for the growth, the excised cutaneous nerves have often been observed to have a free growth with an extensive return of sensibility.

In the return of sensibility after nerve suture, the distance the growing fibrils have to replace plays an important part. Proximal parts show a return of sensibility before distal parts. Again, in the return of sensibility it is found that usually there is first a return of the sense of pain. This sets in in a short time. In a year or longer, the sensation of touch returns. After this comes the sensation of temperature. Space sensation over the skin remains disturbed for the longest time. When the individual sensory qualities are tested by the threshold method, defects are found even after years.

(*b*) Reorganization. For the reestablishment of sensation in irreparable nerve lesions, there is to be considered, in the first place, the wide overlapping of the distribution area of the individual peripheral nerves. The overlapping fibers of the neighboring nerves in the area of the sectioned nerve bring it about that the sensory defect in an interrupted peripheral nerve nearly always remains behind the anatomic distribution of the affected nerve. The overlapping nerve fibers come to the assistance, in various degrees, of the individual sensory perceptions. Pain perception partakes most.

In addition to overlapping of the nerves, the extremities possess the periarterial sympathetic network, which is capable of transmitting afferent stimuli to the central nervous system. In three cases of total section of the sciatic nerve extending over several years, Foerster found that the sensation of the foot was not entirely lost. At biopsy the nerve was found completely cut, and the strongest faradic current was without effect. On the other hand, all three patients complained of severe pain in the foot when the popliteal artery was being denuded. After extirpation of the periarterial network the sensibility of the foot was abolished. Foerster found a similar condition in a case of complete section of all roots of the brachial plexus.

Partly through the many connections with the different peripheral nerve stems of the extremities, the periarterial nerve net of the blood vessels reaches into these nerve stems, into the plexus and into the spinal nerves. But a part of the periarterial vascular net of the extremities comes with the peripheral nerve stems of the extremities and the spinal nerves, with the vascular net of the subclavian and especially of the iliac and aorta, directly into the gangliated cord.

After eliminating the trigeminus, there is at first a total anesthesia of the parts supplied by this nerve. However, after some time, in some cases as early as in from four to six weeks, some sensibility returns. Peripheral stimuli are still capable of entering the central nervous system through the cervical gangliated cord and the pericarotid vascular net, and through the sphenopalatine ganglion and its connection with the intermedius nerve, or through the otic ganglion and its connection with the intermedius and glossopharyngeus. The upper jaw becomes totally deafferented only when the second trigeminus branch has been cut, resection of the cervical gangliated cord and the vascular network of the carotid has been done and the sphenopalatine ganglion has been eliminated.

The afferent conducting tracts of any part of the body are therefore composed of the main sensory tract, coming from the cerebrospinal nerves, and of the sympathetic and parasympathetic tracts. When the main tract is interrupted, there develops at first a total anesthesia. But sooner or later some sensation returns; peripheral stimuli may pass through nearby tracts. When the nearby tracts are also eliminated, sensation ceases entirely. This fact is important for a surgical procedure. In painful conditions the nearby tracts must not be overlooked.

2. Restitution of Sensibility in Section of the Posterior Roots: (*a*) Regeneration. Although regeneration has been anatomically shown to have taken place, it is not known that through this there was a return of sensibility.

(*b*) Reorganization. The areas supplied by individual posterior roots largely overlap one another. Sectioning of a single posterior root is not usually accompanied by clinically observable sensory manifestations. However, the defect can be detected by the threshold method, which shows a diminution in the number, an increase in the intensity threshold and a fatigue of the sensory points, and a delayed chronaxia. But these disturbances adjust themselves in a few weeks.

It is known that the tactile dermatome is larger than the pain and thermesthesia dermatomes; therefore in sectioning a number of adjacent posterior roots the extent of analgesia and athermesthesia is greater than that of tactile anesthesia. Hence, the adjacent roots in the disturbed area spread tactile fibers over a larger area than the pain and temperature fibers.

The observation has been made in man and in animal experiments that a specific posterior root belonging to a dermatome is represented throughout its extent in each root filament. When only one filament is left on sectioning a posterior root, the effect is the same as if the whole root had been left intact. The entire dermatome preserves its sensibility. By means of the threshold method a certain defect should be discovered, but so far no case has been thus investigated.

When all posterior roots supplying an extremity have been sectioned, such as in the arm from the fourth cervical to the second thoracic and in the leg from the twelfth dorsal to the fifth sacral, the deafferented extremity becomes totally anesthetic. In time, in some cases, varying individually in the length of time and degree, sensibility returns. In most cases the sensibility of the skin is totally lost, but deep sensibility returns. Heavy pressure is perceived and may cause pain. If root resection is performed for the relief of a painful condition in an extremity, after an early period of complete freedom from pain there may be a return of the symptoms.

Recently, Foerster operated on a patient for amputation pain in the left arm. He sectioned the left posterior roots from the third cervical to the third dorsal. After three months of complete anesthesia, there was not only a return of the pain, but also an appreciable return of deep and tactile sensibility.

The question is, then, over what tracts do the afferent stimuli pass into the central nervous system after complete elimination of the posterior roots supplying an extremity? In the first place, afferent sympathetic tracts of the extremity run through the peripheral nerve stems and through the plexus into the spinal nerves and from there through the rami communicantes into the gangliated cord. The vascular net ascending with the arteries, largely by evading the peripheral nerve stem and the spinal nerves, passes directly from the subclavian, especially the iliacus communis, into the gangliated cord. From the gangliated cord these afferent sympathetic tracts pass into the spinal cord; in the arm through the upper thoracic roots, from the first to the fifth, and in the leg through the ninth thoracic to the fifth lumbar. When it is desired to deafferent an arm or a leg and to control the pain permanently, it is not sufficient to section the posterior roots from the fourth cervical to the twelfth thoracic or from the twelfth thoracic to the fifth sacral, but either all the rami communicantes of the corresponding spinal nerves of the extremity (the fourth cervical to the twelfth thoracic, or the twelfth thoracic to the fifth sacral) must also be sectioned or the gangliated cord of the entire area must be sectioned; further, the vascular nets of the subclavian or the iliac connections with the gangliated cord must be removed. Otherwise, all those roots must be removed through which the sympathetic tracts enter the cord; therefore where the arm is concerned, in addition to from the fourth cervical to the second thoracic, from the third to the ninth thoracic must be removed, and in the leg in addition to from the twelfth thoracic to the third sacral, from the ninth to the eleventh thoracic. The posterior roots for the arm (from the fourth cervical to the second thoracic) and for the leg (from the twelfth thoracic to the third sacral) represent the main sensory tracts; the sympathetic tracts represent auxiliary tracts. When the main tract is interrupted, there is at first complete anesthesia; the auxiliary tract may return the function, although differing in individuals in the length of time before its return and in the degree of sensitivity. Interruption of the sympathetic tract while the main tract remains intact produces no sensory disturbance.

However, a part of the afferent tracts do not enter the cord through the posterior roots, but through the anterior roots, as shown by the following observations: 1. Stimulation of the central stump of a sectioned anterior root produces pain in the corresponding dermatome. In this there are many individual differences. 2. The gangliated cord was resected from the sixth to the tenth thoracic. Then the eighth intervertebral artery was ligated. This was followed by severe pain. To control the pain, resection of the posterior thoracic roots from the sixth to the tenth was done. The pain still persisted. There seems to be no way of explaining the route of the pain other than through the anterior roots.

3. In resection of the posterior roots from the fourth cervical to the fifth thoracic, the arm is not totally deafferented unless the anterior roots of the same nerves are also sectioned. The same is true as regards the leg. 4. Spinal ganglion cells were found in the anterior roots (Gagel). The relation of the afferent anterior root tracts to the posterior root main tract holds the same for the sympathetic auxiliary tracts. On interrupting the latter and leaving the main tract intact, no sensory defect develops. The part that it plays as an afferent tract becomes evident when, after interrupting the main tract, the primarily lost sensation returns to a certain extent; when all auxiliary tracts are also sectioned, sensation stops entirely.

3. Restitution of Sensibility in Total Division of the Cord: (*a*) Regeneration: Regeneration of the afferent ascending tracts in the cord is the same as that of the descending motor tracts. In complete section in an anatomic sense, it is without any result. On the other hand, in the case of compression of the cord with complete interruption of the afferent conduction, regeneration of the ascending fibers is possible if the glia tissue between the caudal and the oral part of the cord has remained.

(*b*) Reorganization: Even in complete section of the cord, sensation may return, to a certain extent, to that part of the body supplied by the cord segment below the lesion. Foerster has observed three such cases. In one case the patient had sustained a fracture of the lower leg two years after section of the cord. Severe pain in the leg then developed. This led Foerster to assume an incomplete section of the cord. At operation a complete section was found. Faradic stimulation of the caudal part of the cord produced no pain. In total section the only tract by which sensory stimuli may reach the brain from the part of the body supplied by the lower part of the lesion is the sympathetic gangliated cord.

4. Restitution of Sensation in Interruption of Single Tracts in the Cord: The tracts over which the afferent stimuli ascend in the cord are mainly the homolateral posterior column tract and the crossed posterior horn-anterolateral column tract.

The present prevailing teaching is that only pain and temperature are conducted by the crossed anterolateral tract; on the other hand, touch and pressure sensation make use of the homolateral posterior column as well as of the anterolateral tract; as far as touch and pressure are concerned the two tracts supplement each other, and when one of the tracts is out of commission there is no disturbance of touch and pressure sensation.

After unilateral section of the anterolateral columns it is true that at first the sensation of pain is lost on the opposite side of the body. But with the threshold method, by counting the pain points by measuring the intensity threshold and the chronaxia of the pain points, it can be shown that there is at the same time also a disturbance of the sensation of pain on the homolateral side. Pain impulses are therefore not conducted by the crossed anterolateral tract alone, but partly also by the homolateral one.

As a rule, the total analgesia of the contralateral side caused by unilateral section of the anterolateral tract is not of long duration. Sooner or later the sensation of pain returns, first deep pain and later also cutaneous pain. Visceral pain, as a rule, is not lost in unilateral chordotomy. After section of both sides of the anterolateral tracts, with loss of pain sensation soon after on both sides, pain sense sooner or later returns, again first for the deep tissues and later for the skin. If the homolateral anterolateral tract is to be considered as a factor in the return of pain sensation after unilateral chordotomy, this fails to hold true in bilateral chordotomy. There must therefore be other routes for the conduction of pain aside from the anterolateral tract. Foerster is inclined to assume that the posterior columns are capable of transmitting pain. This he supports by the fact that direct stimulation of these tracts causes considerable pain; a mere touch with a sound in the region of the columns of Goll and Burdach causes considerable pain in the homolateral arm or leg; a touch at the lower end of the medulla oblongata, at a point where Goll's column diverges, causes considerable pain in

the sacral and anoperineal region. Hence, for the return of pain after section of the anterolateral column, conduction through the posterior columns must be considered.

Karplus and Kreidl have shown in animal experiments that, in addition to the long ascending tracts, the gray posterior horn columns, as an association of chain neurons, must also be considered in the conduction of pain. Karplus' experimental evidence is not true for man, but certain experiences suggest that conduction by way of the posterior horn columns also plays a part in man; finally, one must also think of extramedullary afferent conduction for pain through the gangliated cord.

Many tracts, therefore, are engaged in the conduction of pain. The crossed anterolateral tract represents the main tract, removal of which causes an initial hemianalgesia; soon, however, other members of the associated activity are able to compensate more or less for the deficit.

The importance of the homolateral anterolateral column for the sensation of temperature appears to be even greater than for the sensation of pain. In unilateral chordotomy the crossed temperature sensation sometimes is not even lost. Bilateral chordotomy must be done to accomplish this effect. For the return of thermal sensation after interruption of the anterolateral tract, the conditions are the same as for the return of pain.

Tactile and pressure sensibility are conducted by two systems, the posterior column and the posterior horn anterolateral tracts. Interruption of one of the two tracts does not cause complete loss of these sensations. On the other hand, these two systems do not entirely supplement one another, so that with a loss of one there would be no deficit in the sensation.

With isolated posterior column interruption there is considerable disturbance in the space sensation of the skin, and in the perception and spatial interpretation of passive movements.

A point to be noted is that after interruption of the afferent tracts of the cord, the return of sensation after a complete loss takes place first in the anogenital region, and that in the slow progressive effects of noxae, sensibility is more or less spared. It is known that the anterolateral tract, as well as the posterior columns, possess an extensive somatotopic division. However, Foerster is inclined to the opinion that the rapid return of sensibility here is due rather to a dermatome having a diffuse representation in the cord.

5. Restitution of Sensibility in Cortical Lesions: Sudden interruption of a sensory area of the cortex first causes complete anesthesia for all qualities in the area supplied. But in all cases sensibility more or less returns. Restitution follows a topical principle. In complete hemianesthesia, sensation returns to the trunk, beginning with the mesial parts, and still later to the extremities, in which the proximal parts are restored before the distal parts. In addition to the topical principle, there is also a difference in the restorative ability of the different forms of sensation. As a rule, there is first a return of the sense of pain; next come pressure and tactile sensation, and then temperature. As a rule, sensation of motility and position, spatial sense of the skin and the ability to recognize objects by palpation take the longest time to recover. Tactile agnosia may be the only defect remaining in cortical lesions. Foerster does not think, however, that tactile agnosia is characteristic of cortical lesions alone; it occurs also after injury to the afferent tract in any place: in peripheral nerve lesions, in posterior root lesions, in posterior column and temporal lobe lesions and in disturbance of the thalamus. It is apparently one of the finest indicators of damage to the afferent tracts. Apparently, in tactile recognition the cortex is in need of receiving more exact and more finely differentiated afferent indications than in other perceptions. Furthermore, it must not be overlooked that when integrity of sensibility is spoken of, this is only relative. Threshold tests often show defects in individual sensory qualities, when an ordinary clinical examination may show no disturbances.

In restitution of sensation in cortical injuries the fact must be considered that the afferent conducting tracts end not only in the contralateral hemisphere

but also in the homolateral side of the brain. Duner de Barenne has shown this to be true for the monkey, and clinical experience in human pathology speaks in the same sense. Then there is to be considered that the cortical receiving stations of the afferent conducting tracts are much more extensive than is usually taught. In the monkey, Duner de Barenne found that the sensory area includes not only the posterior central area but also the anterior central convolution and the adjacent part of the frontal lobes, and that posteriorly it extends to the upper and lower parietal lobes. These observations have not been substantiated in man. In man, however, the upper parietal lobe should be added to the sensory area. As far as the precentral and the lower parietal areas are concerned, Foerster has never found in man that electric stimulation produced any sensory experience, such as paresthesia or pain, nor has he observed any sensory disturbance in excision of these areas. This does not mean, however, that in man the precentral areas and parietal lobes are not to be considered a part of the sensory area.

When the processes that take place in the restitution of motility and sensation in lesions within the nervous system are observed, one can note that in addition to regeneration, that is, the restoration of lost nerve tissue, the principle of replacement of substance, there also takes place a considerable reorganization of the remaining part of the nervous system, which serves for the restoration of function. All conducting tracts that can be of assistance are engaged; whether they be concerned with afferent or efferent conduction is immaterial; unsuitable connections are omitted, of course; appropriate connections are opened, and forces are mobilized that do not depend directly on innervation, but are based on the fact that all parts of the organism, including the noninnervated, belong to the physical basic laws. All serve the organism in a remarkably spontaneous manner, even though they may here and there be assisted by medical art.

An indefatigable, immovable striving for adjustment rules the organism. The same rule that governs superficial wounds obtains in destruction of nerve tissue. There is a tendency toward replacement of substance, and when this is not possible, at least a replacement of function is attempted. Every biologic happening in the organism and every happening in the nervous system, whether they are concerned with a voluntary movement, involuntary reflex movements or with afferent stimuli from the body periphery to the central nervous system, have a definite usefulness. And when the nervous system becomes deranged through sickness, the organism possesses and finds ways and means to serve the purpose of the moment.

RESTITUTION IN INJURIES OF THE BRAIN CORTEX. DR. K. GOLDSTEIN, Berlin.

Two problems, not sharply differentiated, are to be considered in the question of restitution: the problem of restoration of a lost function in a brain defect by the entrance of another system into the function of the part destroyed, and the problem of the manner of disappearance of a functional disturbance caused by a brain lesion and the replacement of a lost function through others. The first problem is principally anatomically or locally oriented. Still it is considered for the fact that in an organ, the individual separate parts of which are assigned definite functions, a part may take over a function that originally did not belong to it. The second problem can be studied through clinical observation, independent of the question as to the relation of function to a definite center, and especially the relation of the disturbed function to a definite lesion; the anatomic facts come into consideration only in so far as the manner of rebuilding and replacement are largely dependent on the position and extent of the lesion, recognition of which is important for proper judgment as to the possibilities present in a concrete case. The first problem is bound up with the entire complexity and unclarity of the problem of localization. The principal contrasting conceptions of localization are not of great importance in the problem under consideration. Whether the standpoint taken is that a circumscribed, localized, individually limited function exists or that each function is an expression of a definite stimulus of the entire brain,

even of the entire organism, the difficulties remain the same. Perhaps the latter conception offers somewhat lesser difficulties. As will be noted, the taking over of a lost function by the remaining tissues to a certain extent is more understandable than the old theory of localization.

Disregarding entirely the fundamental differences in the teaching of "localization," and considering what facts are present for deciding the question of restitution, that is, the return of the old function regardless of the presence of a defect, there loom up first difficulties based on the lack of the anatomic and symptomatologic considerations that are necessary for a decision whether restitution is present or not.

The lack of anatomic consideration is based first on the meager knowledge concerning the relation of circumscribed areas of the cortex to definite functional disturbances or to functions, and concerning the importance of the entire remaining part of the brain, or even of the entire organism, to the performance of a function. The consideration of lesions has been altogether too schematic; little consideration has been given to the more delicate types of injury to the tissues and to the greater or less extension of the lesion to individual layers. These are anatomic considerations. Not only is the simple establishment of anatomic changes methodologically limited, but the precise answer to the most important question as to what relation exists between a definite kind of anatomic substrate and a definite function is practically impossible. Has the remaining substrate sufficient power to carry out a definite performance, or has it not? Only when this question can be answered will it be possible to decide the question of restitution; namely, in the return of a function can the damaged substrate really be considered as capable of function with reference to the performance in question? To decide whether it is so or not encounters difficulties from the fact that, from a strictly localized point of view, the course of a function, even normally, does not depend merely on the constitution of a definite local histologic relation, but also on the circulatory relationship, on the constitution of the rest of the brain and, as Goldstein believes, on the constitution of the entire organism, for the importance of service to the organism. Special difficulties and uncertainties regarding restitution are based on a lack of knowledge regarding the relation of the "other" hemisphere to the functions of the active hemisphere. This problem demands special consideration, since the assumption of restitution by means of the corresponding area of the other hemisphere is extensively recognized. The main difficulty with this conception is that in a given case it is impossible to know how much the "inactive" hemisphere had not always been cofunctioning, especially in restored function. In a patient in whom this was the case, one should not speak of restitution, but rather of the taking over of the entire function by a part of the appropriate apparatus, since it is not a question of the taking over of a function by a substrate that formerly was not engaged with this function.

Since nothing definite can be said regarding the cooperation of the two hemispheres in the individual functions or in a concrete case, it is clear how unsafe a decision may be as to whether restitution is present or not in a given case.

Monakow expressed himself against the assumption that the other hemisphere replaces the damaged one in a function. He pointed out that the stimuli corresponding to a definite process are self-developed products of a long and definite chronological course which takes place within the total development of the individual, and that this cannot be repeated. Goldstein, while generally agreeing with Monakow, cannot exclude, to a limited extent, "replacement" by means of "relearning." Such a moderate unfolding of self-development of a function could to a certain extent be present in addition to the normal development of the individual, and when it is present could bring about the restoration of a lost function. As an example may be mentioned the presence of a brain defect acquired in childhood at a period in development when the function in question has long been developed. Here a new acquirement may take place, because the child's brain is still capable of new learning which corresponds to chronological development. The same is observed in adults when systematic exercises are carried out

for a long time. Goldstein observed the regaining of function in brain injuries after long and toilsome exercises. This regaining of function approaches the normal only in children. In adults it is always more or less incomplete. This indicates first what the adult brain is capable of learning anew in regard to function, and through a number of characteristic peculiarities, which the newly acquired functions demonstrate, it offers a possibility of differentiating newly learned functions from those that have merely returned. For the question of restitution it is important to recognize restored functions by their special characteristics.

The relearned function need not occur by making use of so-called reserve material. There is no proof for such an assumption. General biologic considerations permit the assumption that only the remaining part of a definite apparatus has the power of relearning. The fact that the perfection of a renewed function may vary greatly with different individuals and with different functions would also indicate that the reserve material does not enter into consideration, but that the other side of the apparatus, the other hemisphere, influences the different degrees of perfection in return of function.

The difficulty in deciding whether restitution is present becomes further increased by symptomatologic consideration. As long as it was assumed that individual functions are independent among themselves and that each one is dependent on the integrity of a definite circumscribed substrate, the sure symptomatologic establishment of a defect, especially its restitution, must appear simple. But it has been found that the assumption of individual functions and circumscribed loss of function is untenable and was made possible only by a misunderstanding of the true manifestations. The symptomatology even in definite circumscribed injuries is complicated; the disturbance embraces more or less different functions. To be sure, these disturbances of function do not all stand in the same close relationship to the defect. Monakow has called attention to the principal difference between the initial and the residual symptoms, and to the fact that certain manifestations that appear secondarily as a result of others may be similar to those caused by other defects. Thus, in a lesion of the occipital lobe, as a partial manifestation of so-called mind blindness a tactile paralysis appears as a secondary manifestation. Many mistakes may be made when this fact is not considered. One of the mistakes is the failure to distinguish between a real return of the former function and only an effective fulfilling of a task, which on superficial observation may impress one as a return of the old function. For example, a patient with tactile agnosia, who at first was unable to recognize any object, in the course of time was able to recognize a number of objects; nevertheless at autopsy a marked defect was found in the characteristic site. One would be inclined to assume a restitution through the opposite hemisphere. When the facts are carefully studied, however, it is found that in reality recognition is disturbed now as before, and the patient has learned his tasks by making better use of a roundabout method, namely, the intact former recognition which was present to start with. A critical consideration of the anatomic and clinical facts permits the conclusion that proof of the operation of a substrate to assume a destroyed function that it formerly did not possess offers many difficulties, which apparently cannot be overcome. Definite evidence for the assumption of a real restitution is not present. It must also be denied that one part of the brain can substitute for another part, that latent material can take over the function of destroyed tissue and that the corresponding opposite hemisphere can replace the damaged one. A true return of function takes place only by the reestablishment of the substrate or, under definite, rare and limited circumstances, through painstaking reeducation with the assistance of the remaining part of the substrate which had already been of service in the function. The acquired functions are usually incomplete, especially in adults.

Whenever restitution appears to be present, it usually means either that after a lesion, limited to a circumscribed area, a recession of the pathologic anatomic process occurs and the diaschisis recedes, or that the problem is overlooked and

the anatomic and symptomatologic considerations are misinterpreted. In false restitution there is not a return of lost function; there is only a substitution. This substitution plays a prominent part in brain defects. Its importance lies not only in the fact that it permits insight into the function of the organism, especially with reference to the manner in which it acts when a defect is present, but also in that it points the way to procedures for reestablishing functional ability in cases in which it has been lost even for a long time. In fact, this is the main problem in the field of restitution.

Two types of restitution are to be distinguished: One is found in lesions of the so-called peripheral cortical areas, that is, in the projection fields of the motor and sensory areas, and the other in lesions of the so-called higher centers. In the former, improvement takes place through a changed connection of remaining functions with the activities of the outer world; in the second, the losses are replaced —only partly—by other functions.

As an example of the first type, Goldstein cites the case of a total and permanent destruction of the calcarine area. The customary visual field test shows the unchangeable picture of hemianopia. The corresponding retinal area has become visionless. Yet the patient's vision need not be limited to half of the field. It is well known how little disturbance a hemianopia may cause. The facts are that under all conditions other than the usual perimetric test, patients, like normal persons, see in all directions; vision is grouped around a central point; the point of acute vision lies in the center of the visual field, as in the normal state, and not on the border of the visual field, as it appears in the perimetric test. The entire visual field may not be present soon after a lesion, and when this is observed the impression may be gained that a restitution has taken place. How is vision possible in the entire field in the presence of a defect in the calcarine area? Fuchs, who investigated the subject experimentally, came to the conclusion that the activity of the visual apparatus has changed. Where formerly one calcarine conveyed the vision of one side of the outer world, it now conveys also that of the other side. The eyes turn slightly to the side; the stimulus that falls normally on the present corresponding blind portion of the retina now falls on the seeing part of the retina. But to disregard the deviation of the eyes and to consider only the changes that must take place in the calcarine in order that the entire visual stimulus may be represented: The apparatus must be so changed that the remaining part gives the same service as did formerly the bilateral apparatus, and that it is capable of taking in, from all sides, the entire visual field, which groups itself around a center as in normal persons. To those who hold the conception that the normal visual fields require stimulation of individual parts of the retina, more so the calcarine, this change is unintelligible. The formation of the entire visual field is not bound only by the activity of the calcarine, but the calcarine rather adjusts to a certain extent the relation to the outer world. The visual field is a manifestation of the activity of the entire brain. This relationship—to a certain extent, the creation of the material—apparently does not depend as much on the condition that both halves of the retina, any more than the calcarine, should be stimulated, but rather on how stimulation occurs. If the functional half of the visual field is stimulated in a way corresponding to the normal field, that is, as occurs when the viewed object appears within the stimulated surface, then a single calcarine is capable of arranging the material for producing a whole visual field. What has changed from the normal is only that the organism has adjusted itself to the stimulation of the material present in one calcarine, as it formerly was adjusted to the stimulation of both calcarines. This type of readjustment of the organism in a defect of a peripheral part of the brain is found not only in lesions of the calcarine area, but also in other sensory and motor spheres. It plays the chief rôle in relearning in transplantations; also in the return of speech in some cases of motor aphasia, there is often a readjustment such that the remaining part of the motor speech area of the other side is able to take over the function of adjustment to the peripheral motor apparatus, so long as central speech remains intact.

The readjustment in calcarine lesions is not a voluntary process. It takes place without the patient's knowledge. It also appears suddenly. Even when the patient observes that certain controllable situations bring improvement in his disturbances, it is even then only secondary and the readjustment follows without his knowledge. The hemianopic person observes that, in order to see an object clearly, it is best not to look directly at the object but slightly sideways. This type of vision is voluntary, but is usually accomplished without the patient being aware of it.

Third, the readjustment takes place as a need of the entire organism. If the remaining calcarine area continued to function only in the old way, the effect of the optical stimuli would be markedly changed from the normal, and thus the reaction of the organism would be largely falsified. The organism would find itself in constant disagreement between its optical stimulation and its other experiences. This disagreement, which expends itself in subjective unrest and objective disagreement, is avoided, in that a state is brought about in which the organism finds itself under conditions that require only profitable or useful stimuli, which in the main it is able to overcome, independent of its defect. The condition found in hemianopia represents only a special case that is observed generally in defects, especially in brain defects; it is the tendency of the organism to gain a most favorable situation, and to realize and make use of inborn abilities. It is to be noted that the readjustment takes place only when the defect is complete. When the calcarine area is not completely damaged and is still capable of transmitting stimuli, readjustment does not take place. The patient's visual fields remain as they were, except that one side is better than the other. It is only when the old type of stimuli are no longer capable of being received without bringing about an upset or injury to the normal configuration of the visual fields that readjustment follows. This suggests another rule, which is generally applicable to the changed relation in defects of the brain: The organism retains its old activity as long as it performs to some extent the appropriate function of which it is collectively in need. When this is no longer possible, a readjustment takes place.

It is also shown that such readjustments take place with limitation of function. When the hemianopic person qualitatively has a visual field corresponding to the normal, quantitatively his perception of the outer world is considerably diminished.

Many analogies can be pointed out in other forms of life. A similar condition is found in the sea urchin when a part is destroyed after differentiation has to a certain extent taken place. An animal deprived of a limb remains complete, only somewhat smaller. Everywhere it is found that under biologic forces there is a pooling together of the remaining part of a defective apparatus in order to reach a state corresponding to the old one.

Here one should recall Bethe's experiments in which there was a return of function after the amputation of limbs in lower and higher animals; this always took place in such a way that the best possible results followed. Here, too, the readjustment is sudden and without training, and is apparently due to the tendency to bring about the most favorable situation for the entire organism.

Since the aforementioned restitution develops by itself, without instruction and training, it does not call for therapeutic efforts. It is more important to teach the organism to avoid or, when necessary, to encourage certain relationships.

To demonstrate the second type of repair in severe cortical injuries, the most severe disturbances of all voluntary functions are encountered together with unaffected ones, even though breathing and the heart beat are scarcely normal. There may be only a certain tendency with reference to the grasping reaction as shown in the grasping reflex, the sucking reflex, the primitive tonic sole reflex, the turning in reaction to a noise causing fright, the turning toward light, etc. In such cases the recovery may limit itself to such functions only. Such a condition is observed not only in severe cortical injuries with loss of consciousness, as in concussion of the brain, but also as a persistent symptom after severe encephalitides especially in children.

In addition to a marked reduction of function, such patients show a change in the course of the remaining functions. On the one hand there is an abnormal subjection to an acting stimulus, such, for example, that when the eyes are once adjusted to the stimulus of a light, the adjustment may continue as long as the light does, or there may be a change to an abnormal restlessness. These apparently opposite manifestations, the fixation and the change, are only different expressions of the same fundamental alteration. The restlessness is a special characteristic phenomenon of acute disease, caused by a disproportion between the demands arising from the normal surroundings of the patient and his reduced ability to adjust. In severely disturbed patients nearly all occurrences of the outer world, when they become affective, result disastrously.

The disastrous reactions are therefore especially ominous to the organism, not only because, through them, it becomes momentarily deeply affected, but also because the shock prevents the organism from performing any functions for a shorter or longer time, even those of which it is capable. This holds good for the normal organism and in increased degree for an injured one. Therefore patients in a state of restlessness often perform badly; when it is possible to bring them to a favorable state they are able to perform functions that they could not perform before. Even the normal organism protects itself against too severe catastrophic occurrences of the outer world; it reacts only to occurrences that will not cause too great upsets, only to such as form its milieu; with these it functions and performs in accordance with its natural ability and character; by these its existence is assured. In the damaged organism, because many more occurrences may lead to disaster, protective defense is much greater. This is made possible only by a narrowing of the milieu against the causative condition. Consequently, in order to acquire restitution, it is necessary that the organism should find itself again, in correspondence with its changed being and therefore unlike what it was before, in a narrowed milieu; it is then that regulated relations begin to appear. The change in milieu, as well as the return of the regulated relations, is also a characteristic sign of the appearance of restitution and the return of lost function.

In severe cases little function returns; only a narrowed milieu is adequate. Existence of the organism under these circumstances is possible only by careful protection from fellow men in preventing inappropriate stimuli. The therapeutic possibilities in such cases are few; even these few are possible only by recognizing the functional possibilities remaining and by making use of them. If such a person succeeds in finding a situation adequate to his needs, it is often surprising how much he is still capable of accomplishing. A restitution takes place in the form of greater cleanliness, in movements, etc. The patient can be kept at rest, although at times the aid of a narcotic is required.

What is observed as characteristic of restitution in severe cases is also true in other cortical lesions even though the symptomatologic pictures may vary in individual cases, principally because a greater return of function takes place in circumscribed lesions, especially those in a single area. Milder injuries offer insight into the manner in which definite functional defects may be replaced by other functions. They also make clearer some other general observations.

In a disturbance caused by a brain lesion it is not a question of the loss of isolated functions that have been learned, but rather the loss of definite functions, definite reactions and behavior reactions of the organism. The single function is impossible because the patient is incapable of utilizing the behavior activity. At the same time the cases with loss of memory only play a minor part. Moreover they also require a different explanation from those caused by circumscribed residual lesions. The dependence of individual functions on behaviorism appears especially when the disturbance is not so severe and the defect is more circumscribed, and in the course of recovery, a definite behaviorism returns; then suddenly not only are individual functions possible, but a large number of functions return, namely, all those that require restored behaviorism. It is repeatedly observed during reeducation in aphasia that suddenly the patient is capable of

using words, not only those he has relearned but also other words. This takes place when one succeeds in bringing about something like a definite adjustment with the aid of training. From a therapeutic point of view, it indicates that it is necessary first to help in the recovery of the lost behaviorism, which is not always successful without a recovery from the process taking place. When this does not succeed, it is useless to bother the patient with training that can succeed only when the lost behaviorism has returned.

The breaking up of function in cortical injuries, including the circumscribed ones, generally proceeds in such a way that the more complicated behaviorisms suffer first. Spontaneity, voluntary and "objective," and imagery suffer first. Freedom of decision suffers. It is only another form of change when the reactions of the organism depend to a larger measure on the occurrences of the outer world than was formerly the case, and when they are more difficult to separate one from another and from the general situation. In this larger subjection, the organism is torn away by a change in the outer conditions. To a certain extent this subjection and these changes remain, even though considerable reparation has taken place, as long as the defect has not been controlled. To some extent order and rest suffer even in circumscribed defects, regardless of the presence of repair.

Frontal lobe lesions in many respects resemble general severe lesions of the cortex. In cases in which single functions are fairly well preserved, damage to one of the basic relations is especially found. Disturbances are found in the power of thinking, speaking, volition, the sense of feeling and the appreciation of time and space; everywhere retained functions are present, but only such as require a primitive behaviorism. If one succeeds in bringing the patient into a milieu in which only such functions are required as those which to a certain extent are self-developed from the situation, while limited in his milieu, he is quiet and not much disturbed. This can be observed repeatedly in brain lesions, and in some cases of severe brain lesions the patient can be made to perform useful acts.

In lesions of the optical sphere (so-called mind-blindness) a similar injury of the fundamental relations is found, but is especially marked in functions that come from the realization of optical material. All functions of the optical sphere requiring a simultaneous realization are nonrestorable, but those requiring successive functions are retained better. In some cases the restitution may be exceptionally extensive; the successive movements may be so rapid and shortened, and follow in such quick succession, that they may elude the untrained observer. With practice the patients may become highly proficient in the use of their motor ability, so that they may even return to a former activity. In so-called cortical motor aphasia, the injury shows itself especially in the case of definite function in motor speech. In addition, there are alterations in other spheres, as in writing, in motor calculation or in the function relating to time and space, but all of these are to be considered as an expression of the same fundamental change. Restitution in such cases can take place by making use of speech "series" functions and especially by calling in the aid of functions from other spheres, such as the optical. Thus one may explain certain forms of paraphasia, in that the patient, who in writing normally depends on the words spoken by himself and who is now incapable of speaking, makes use of optical word pictures, which appear involuntarily and which normally are lacking, bringing about a corresponding mistake in writing. Therapy would have to depend on the improvement of the represented optical picture.

Observations on the conduct of the organism in the presence of definite defects, while at the same time retaining other functions, permit the recognition of a general law which seems to be of great importance. Observation in calcarine defects have shown that restitution does not always take place, but when the disturbance subsides, function being sufficient to a certain extent, the organism maintains its old behaviorism, is satisfied with the insufficient function and does not create any changes. There takes place, therefore, a kind of selection of different possibilities. The kinesthetic sphere is used to replace the disturbed optical sphere

in mind-blindness only when severe mind-blindness is present and not when the optical sphere is still sufficient for many functions.

For the creation of function, energy distribution is of greater importance during sickness than in health. The greater difficulty in certain functions caused by lesions in definite areas necessitates for their performance special energy which can be gained only when other functions cease.

Observations in partial and total calcarine lesions permit the recognition of certain points of view that prevail in selection. Thus, it is observed that selection takes place with the object of maintaining as much as possible the old manner of working. A similar condition is found in the aphasic person when he makes use of his incomplete speech in order to make himself understood, instead of selecting gestures for that purpose. In themselves, gestures would perhaps require less effort, but they would require a complete change of the general relation, such as takes place only when no function is possible in the old way, so that the organism would be most severely disturbed. There then appears to be present a kind of leveling according to need, by which relation the organism is kept less disturbed in the performance of its essential functions. This is maintained according to the possibilities. This points to an important fact in the selection of functions, namely, the more or less great importance of a function for the general conduct of the entire organism, that is, for the realization of the task that belongs to the organism, the making up of its "being." The individual function of the organism forms a graded ladder and possesses different values, according to which the possibility of selection follows. Complete permutation, namely, restitution through heterogenous forces takes place only when the old relations would disturb the collective relations more than the entrance of one new, even though only relatively useful restitution.

The selection not only appears to follow the object of function, but also tends to prevent dangerous reactions. This factor enters as it were in a negative sense: The restitution develops better the more the patient, regardless of the defect, is capable of performing the most useful functions and the less he needs to fear bad results. This becomes understandable from the point of view of the distribution of energy and the relative energy constant.

Selection, therefore, is decided by the fundamental tendency for maintaining those functions which, from the point of view of the collective relation, are most important, hence the most essential ones and those that are best accomplished in relation to the outer world. Under such conditions the quantity of energy present is used to the best advantage.

It is evident that restitution depends a great deal on the condition of the body as a whole, on the general strength. It depends not only on the condition of the brain as a whole, but also on the condition of the rest of the body, on the circulatory condition, etc.

Goldstein summarizes as follows the main points that he considers in relation to restitution: 1. Real return of former function takes place only when complete anatomic restitution takes place. 2. If complete anatomic restitution does not take place, there is no return of function, but repair. 3. Repair is recognized by a number of characteristics. The following are always present: (*a*) A greater breaking up occurs, corresponding to the damage in the function; (*b*) the functions are changed in a qualitative way; the reactions in a definite milieu are more constant and the stimuli more bound; in changeable stimuli there is a greater inconstancy of the reaction than in the normal; (*c*) rest and orderliness of control are easier than in the normal, and more readily disturbed. 4. An orderliness in qualitative normal relation in this sense is observed only by a narrowing of the milieu, in finding an adequate milieu for the disturbance. Then the orderliness and rest are even greater than in the normal. 5. The restitution picture depends on: (1) the total capacity of the organism before the disease sets in (the amount of former ability and especially of the functional quantity); (2) the greater or lesser degree of inviolability that the entire organism can withstand (circulation of the blood, general condition of strength, etc.), especially in regard to the brain;

(3) the energy present for the use of a function, which as a result of the relative constancy of the total energy is dependent also on the use of energy in other places; this results in the retaining of certain functions at the cost of others. The selection is determined by the tendency of the organism to maintain those functions which, from the standpoint of the total task of the organism (its nature), are the most important, and, among the most important ones, those best capable of accomplishing the given objectives of the surrounding world. The favorable result of restoration is therefore dependent on: (4) the milieu in which the particular organism is living, as well as on the demands being made. A defect is the more restored the more the organism is capable of reaching its surrounding world with the restitution.

From the foregoing considerations one learns a definite therapeutic procedure, which must be considered as a general rule: Never attempt to improve a definite disturbance in itself; its importance must always be considered as a task for the entire organism, for the corresponding nature of the organism, the more so as the nature is altered by the illness, and the therapeutic measures are to be determined from such considerations. An attempt is to be made to bring the patient into a situation in which an adequate milieu may develop for the changed organism; in which the organism, regardless of the defect when compared with its former being, may perform its most useful functions, and in which it can work as regularly as possible without the intercurrence of too severely catastrophic reactions. When this is accomplished, the organism, although not normal, is none the less not sick. Subjectively it feels well, and objectively it shows little disturbance. This condition appears as the goal in the process of restitution; it must also form the object of any therapeutic attempt. From this it follows as the most important negative problem that one should not proceed therapeutically with certain symptoms, because an organism, thus functionally more able, will "recover better" than when attempts are made to control all symptoms. The task is therefore to determine which defect is to be controlled and which is not. The scientific considerations of the manifestations, however, are not sufficient for such a decision; a comprehension of personality in its essence and a willingness to enter into the personality of the patient are essential here.

ABSTRACT OF DISCUSSION

Dr. G. Anton, Halle: Four compensated brains were observed. In three cases compensatory hypertrophy occurred in defects of the cerebellum, and one in defect of the brain. Case 1 was that of a girl, aged 6½ years, with complete absence of the cerebellum. A cross-section through the medulla revealed a high grade hyperdevelopment of the pyramidal tracts and of the lemniscus belonging to it. The funiculi gracilis and cuneatus also were enlarged and clublike. The same was true in the higher regions of the trigeminus, including the locus caeruleus. The olives were atrophic; Deiters' nucleus was small. Case 2 was one of unilateral absence of the cerebellum. The pyramidal tract, on the side on which the cerebellum was present, was greatly enlarged, as were, to a lesser degree, the sensory tracts. It is interesting that the decussation of the pyramidal tracts began in the pons. Case 3, reported by Monakow, was that of an idiotic child, aged 3 months. The cerebellum was entirely absent. The pyramidal tracts and the region of the lemniscus showed hypertrophy. Case 4 was one of porencephaly in the left temporal lobe; it showed enlargement of the other side in the stem as well as in the brain. It is to be noted that in cases 1 and 4 the cortex also showed enlargement.

In addition to these cases, it should be recalled that a case of chorea was reported in which the dorsal half of the putamen was destroyed and replaced by characteristic myelinated fibers. It appears from this that the degree and the location of compensation can be measured by the proved hypertrophy of other functional systems. Enlargements of other parts of the brain, especially of the cortex, need not necessarily be caused by compensation in function. Case 3, how-

ever, shows that the fundamental relation between the individual systems may show itself as early as in fetal development. The laws of compensatory enlargement in the brain, inclusive of the brain stem, should be different. It must be observed that, especially in the brain, the specific initiation for growth would even be lowered and diminished, since the stimuli coming through the corpus callosum of the injured side were interrupted and diminished. As regards the case of chorea with destruction of the putamen, I agree with Spatz that the destruction and the compensation following in the brain stem, especially in the extrapyramidal systems, have been assumed as altogether too local. I have always maintained that in the chorea the functional disturbance is not due alone to the striatal disturbance but also to a disturbance in the relation between the two large basal ganglia, the thalamus and the lenticular nucleus. The symptoms of disease of the thalamus differ from those of disease of the lenticular nucleus; in the former, the automatic and mimic activity is diminished; in the latter there is a loss of inhibition. Lesions in the thalamus may not only bring about loss of function, but may also bring on irritation; hence, eventually chorea may develop, which is ordinarily caused by a loss of inhibition in the striatal system. Regarding the question of compensation, the cases cited indicate that it is not a question of increased single conducting tracts, but rather of inner functions and the growth relations with other brain complexes, especially the brain cortex.

DR. VON WEIZSÄCKER: A comparison between the nonanatomic papers raises the question whether the opposing views, especially those of Foerster and Goldstein, are only of different considerations or whether they represent irreconcilable contradictions. Roughly, it can be understood that Foerster assumes a reorganization in the sense of the taking over of functions by noninjured areas, while Goldstein denies this. In discussing these views it is recognized that not only are the results different, but the manner of observation, thoughts and scientific theories are primarily different. This also expresses itself in the fact that the readers of the papers have taken to definite forms of teleology, though in different ways. From a scientific point of view the arguments produced must be declared insufficient, and the discussion of the problem again becomes necessary. One point to be raised, is whether there is an exact scientific method of measuring in physiology. When it is desired to localize functions, it must be established what a function is and how it can be investigated. A patient can be examined for objective performance. This can be done in two ways: (1) One can observe acts of perception or action and judge and describe them as a solution of a problem; (2) under variations of the problem, one can undertake a measurement, and decide thresholds and limits. Instead of an analysis of performance one can undertake an analysis of function. The question is raised: Can the establishment of time, space and intensity values also be applied to the pathophysiology of central disturbances? This can be answered in the affirmative. It has been found that those changes which in the periphery were called the reaction of degeneration, that is, a formal change in the stimulation process as it relates to time and intensity, are also present in central disturbances; this explains in an elementary, formal and general way the breaking up of many functions. From this standpoint Goldstein could proceed further and could say: In principle, under pathologic conditions there is no "new acquirement" other than that which always existed; it is only worse. For it is known that in well persons the disposition of life adjusts itself from situation to situation, each time to new problems. That which appears as different in pathologic conditions is not a building up, newly acquired, or a reorganization, but rather a manifestation of the breaking up in a lesser disturbance. It can be added that an exact scientific investigation and analysis are known only as far as the breaking up and not as far as the building up of the function.

DR. JOSÉ MA DE VILLAVERDE, Madrid, Spain: The most important fact in regeneration is the development of young branches in the central stump of the axon which, after passing through the cicatrix, innervates the peripheral stump of the sectioned nerve. This occurs not only when the nerve is sectioned but also

when it is compressed or tied. Even when the sheaths are not cut the axons produce small branches which possess the tendency to proceed to the peripheral parts of the sheaths. The regenerative ability of the axons is clearly observed in toxic or infectious neuritis. Here the problem varies. At first there is the cause of injury to the axon, through the blood stream. Second, it must be remembered that the cell of the affected fiber in the anterior horn of the cord is diseased, since it is affected by the toxin coming through the blood stream. Nevertheless, its regenerative powers are considerable, as histologic and clinical examination show. In cases of neuritis, the fiber regeneration takes place differently from what it does when the nerve is sectioned. None the less, what occurs is fundamentally the same. Some axons break at a point where the toxin enters. In such cases it often happens that the starting point of the axon branch is found above the breaking point, and from here on it runs inside the sheath. When the axons do not break, the lesion brings about the production of branches. They are lateral and turn around the axon. The axon possesses considerable ability to produce branches, even in cases of neuritis and when the tissue is destroyed. In strongly intoxicated nerves the production of young branches is scanty. But the axons that give the impression of having nearly lost their vitality are capable of producing new branches when the nerve is cut through. This type of lesion is most favorable for the production of young branches, and in cases in which other lesions do not give this result. In neuritis produced in the rabbit by subcutaneous injections of blood, after the neuritis became intense and the nerve then was cut, it was found that some of the axons that were considered to be nearly dead showed young branches. This is not true, however, for all fibers. In some it is observed in a slight degree; in others the phenomenon cannot be noticed. When a nerve is sectioned, the young branches developing in the central stump go through the cicatrix into the peripheral stump and innervate the latter. How it passes through the cicatrix and the conditions required for it to reach the peripheral stump have been described differently by different authors. Some investigators, who agree with Marinesco and Nageotte, affirm that the young branches that develop in the central stump are incapable of reaching the periphery. According to other investigators, including Ramón y Cajal, the newly formed branches at the central stump run through the cicatrix area entirely independently, and in this way reach the peripheral sheath. When one studies the different phases in the experimental sectioning of nerves it is necessary to observe what takes place in the first days of regeneration. It can be observed that the young branches run freely between the connective cells and the exudate of the cicatrix. This can be observed with pyridine fixation. After three or four days, the young branches run free without the conducting cells, but some attach themselves to the fibroblasts of the cicatrix. This is a stereotropic phenomenon. In six or seven days, the young twigs, after they pass through the cicatrix and until they reach the peripheral stump, are protected by a large number of cellular elements. It is believed that the cellular elements are important in permitting the twigs to pass through the cicatrix. The nature of the cells accompaning the young twigs is unknown. It is questionable whether they are Schwann's cells. A number of facts speak against it. These cells cannot come from the central stump. The division of these elements of the central stump, which is limited, supports this view. In lead-poisoned nerves the Schwann cells are extraordinarily damaged, diminishing to a considerable extent their proliferating ability. Yet, after intoxicating the rabbit and sectioning the nerves, after fifteen days it was found that in the area of the cicatrix the young large twigs were protected by the aforementioned cellular elements. The clubs that were formed were surrounded by the same cells. The technic employed in this study is not appropriate. Cajal is in considerable doubt as regards the origin of these elements. In the peripheral stump the young twigs, originating in the central stump, run through the solid or the crypt, a virtual cavity of the Büngner cell bands, but not through the protoplasm. A few young twigs course between the cell bands. The widespread conception that every young twig runs in the

cell bands is correct, if it is pointed out that the structures mentioned possess in the middle a virtual cavity through which the young twigs course. The peripheral ends of the young twigs are club-shaped; this enables them to enter into the peripheral stump.

DR. L. GUTTMANN, Breslau: Compensatory possibilities in disturbances of the sweat reaction can be well studied with the aid of Victor Minor's method. It is immaterial whether the disturbances of the sweat secretion are peripheral, medullary or cortical. In total interruption of peripheral nerves, when there is an anhidrosis in the corresponding skin area, there is an increased sweat secretion in the area of the proximal nerve. This perilesional hyperhidrosis is observed more intensely at the border of anhidrosis after injections of pilocarpine. In some cases of anhidrosis a compensatory hyperhidrosis may develop in the corresponding part of the opposite side of the body. In medullary and cortical lesions there can also be found perilesional hypohydrosis or hyperhidrosis at the border.

DR. HALLERVORDEN, Landsberg: In the ganglion cells in developed brains neither amitotic or mitotic division has been observed. Division also is not found in ganglioneuroma of the brain; the tumor elements are only glia cells. Likewise, in ganglioneuromas of the sympathetic there are no definite division processes to be recognized; the ganglion cells develop anew from the cells still remaining that are alone capable of division, namely, the sympathetic forming cells.

DR. B. PFEIFER, Halle: In puncture of the brain of adult man with a cannula, the damaged area is filled up by connective tissue and not by glial tissue. In preparations stained with Weigert's method no glia fibers can be found. On the border of the cicatrix there are fibrils that show considerable branching and clublike formation. In very old cicatrices (ten and one-half months) the fibrils are also covered with a medullary sheath, which appears to indicate that they have regained functional ability.

DR. REICH, Berlin: I agree with Boeke as regards the anatomic histologic structure of nerve fibers. I see in this a confirmation of the cell-chain theory, with which I agree on the basis of my studies of the microhistochemical observations concerning the protagon myelin type granulations of the nervous system and the distribution of the neurokeratin in the nerve fiber. It is not correct always to speak of cells of the Schwann sheath. The cells that form the cell chains in highly developed nerves reach from one intra-annular segment to another. The Schwann nuclei, each of which corresponds to an intra-annular segment, are not nuclei of a sheath which surrounds the nerves only on the outer part, but are exactly like sarcolemma nuclei of muscle, as muscle cells are. Not only are these nerve fiber cells composed of a sheath, a nucleus and some surrounding protoplasm, but to them belong also the myelin, axis cylinder, neurofibrils and in fact everything that lies in the intra-annular segment. They are the builders of the nerves; they degenerate when the nerve degenerates, and they again build the nerve in regeneration. It is a question whether the neurofibrils of the axis cylinder are to be considered also as a product of the cell, or only as an ingrowth of a foreign nerve fiber cell originating from a ganglion cell.

DR. NIESSL VON MAYENDORF, Leipzig: Regarding Boeke's paper, the neuron theory is not supported by the observations in secondary degenerations, and it does not appear to be of any value for the recognition of a special conducting course. After destruction of the calcarine, the cortical visual field as well as the temporal cortical hearing area, it is found that there is a descending and not an ascending degeneration of the sensory tract. Only when a sensory tract is interrupted in its central part from the subcortical ganglion to the cortex does it degenerate centripetally.

As regards Spatz' paper, I was able to demonstrate spots in the cortex, in the neighborhood of an extensive softening, where the ganglion cells around the arterioles were destroyed. In Weigert preparations, newly formed medullary fibers were not found in the destroyed area.

Regarding the paper by Foerster, Foerster's opinion is based on experience, and his conceptions are the result of positive observations. The demonstrated hypertrophy of the pyramidal tract extends to both tracts and not only to the uncrossed one. If the hypertrophied pyramidal tract replaced the lost function, the functional restitution must have taken place through the other hemisphere. Foerster's calling attention to the sensory systems of the sympathetic and of the parasympathetic is most valuable for the practice of neurology.

Concerning the paper by Goldstein, I do not know of a recovery of hemianopia in complete calcarine destruction. I ask therefore whether the involved calcarine region was studied in serial sections and found destroyed in all parts.

Dr. Winkowski, Zurich: Several points have been stressed: Much has been said about the unity of the organism and its importance in the restitution of functional disturbance. This importance cannot be minimized in any way, but one would wish that when this conception is used to explain physiologic and especially pathologic phenomena, it would be rather more precise. An important component appears to be the historical development, which has not been sufficiently stressed in the papers. It was Monakow's opinion that in analyzing the subject under normal as well as under pathologic conditions, a great deal of consideration should be given to the factors of time and space, the genetic development and the building up of the functions. Above all, the cell from which the organism develops forms a natural and complete unit. Further development is characterized by the fact that from this unit, and from within it, there are formed special conductions and mechanisms in anatomic and functional relation, in definite successions and a definite building up, in a progressive differentiating sense, with division of labor, etc. A point to be mentioned with regard to the neurophysiology of the human fetus is the changes in the mode of conduction in the central nervous system in the course of development. In the early stages of fetal development the conduction of nervous stimuli is characterized by a great tendency toward irradiation and a generalization over the entire fetal organism. In later fetal and postfetal stages there develops more and more a tendency toward the concentration of nervous stimuli to definite parts of the nervous central organs and of the body, for the purpose of developing definite optimal conducting tracts and specializing and localizing reflexes, motor and sensory functions, etc. At the same time the original fetus, that is, the almost unlimited irradiated and generalized conducting type, is not lost; it is only more and more obscured, but under certain conditions may again come to the surface. This brings about a complicated condition which at times may disclose essential elements for opposite relations of irradiation and generalized tendencies, on the one hand, and of concentration and localization tendencies, on the other. When the main problem of development consists in how, within a given living unit, definite structures and mechanisms develop, the main problem of physiopathology of the nervous sphere must take into account how, under definite pathologic conditions, by the presence of certain definite local and momentary defects, the function can be reestablished, as far as it may be reestablished at all. It is clear that here one must always take into account factors pertaining to the whole organism as related to some of its parts, and it is not easy to bring them together in a true relation; yet this is important. Another factor repeatedly mentioned is the "objective striving." The question of finality of living things is an old one. Either it is desired, with the stressing of objective striving, to assert that biologic processes proceed as if they were directed toward a goal—when the question must be raised on what it is based: on what special conditions, developments and arrangements within and without the organism such an objective gives indication of usefulness, which leads to the ordinary consideration that has proved so useful, especially in natural science. Or biologic occurrences in the organism are said to be determined by something that lies outside itself and its material surrounding; thus one turns to the field of metaphysics and even to mysticism, which may well be in harmony with one conception of the world, but is hardly suitable in natural science. Finally, harmony is repeatedly

spoken of. To this it may be said that in biologic processes there is indeed a chance of harmony, but there is no preestablished or assured harmony. When this biologic process is considered as a whole, this chance may also be considered as prevalent. At times it is found, but at times not. Regarding Foerster's statement of restitution in motor and sensory areas, it is to be observed that when in interruption and degeneration of a pyramidal tract the other one becomes hypertrophied, this does not have to be considered a compensatory hypertrophy in the narrower sense, that is, in the sense of the taking over of functions for the failing limb or for the part of the body that it normally supplied. It may also be that since the extremities of one half of the body are hemiplegic, the others, especially the nerve tracts, are called on for greater activity than under normal conditions. The indication for this is that cortical representation of sensibility includes a large area; it extends much further than merely the posterior central convolution. It has been found experimentally that cortical representation of sensibility, in addition to the posterior central convolution, must include also the area of the parietal convolutions and that around them. and also the anterior central convolution, the latter in a special sense, as representative stations for so-called unknown deep sensibility (Monakow) or reflex sensibility. At any rate, anatomically it can be said with certainty that in addition to the posterior central convolution and the parietal convolutions, the anterior central convolution possesses a powerful corona radiata of corticopetal projection fibers from the thalamus. Therefore it can in no way be considered as a pure motor area, but rather forms a sensorimotor, and at the same time associative and commissural area. Furthermore, this is true in other areas of the cortex and appears to correspond with a general plan of construction, whereby each part of the cortex originally and in principle is supplied with projection fibers of a centrifugal as well as of a centripetal nature, and also with association and commissural fibers. The general plan of construction is retained everywhere, even though individually, especially with reference to the contrasting relations of the different fiber groups, there is considerable differentiation between the different cortical regions. It is an instructive example of an extensive localized differentiation and specialization proceeding from the same substrate.

DR. WALTER, Bremen: Bethe experimented with vertebrates (especially dogs) and found, after extirpation of a large piece of nerve and most probably with isolation of the stumps, that after some time myelinated nerve fibers appeared in the peripheral part, although it was impossible to establish a connection with the central stump. Since Cajal's and Bielschowsky's axis cylinder stains have been introduced, Cajal has shown that regeneration follows by means of central connections. My own experiments lead me to the same conclusion; and as far as can be observed, other investigators on vertebrates have not observed an autogenous regeneration in the sense of Bethe. On the other hand, Cajal has gone too far when he speaks of a "free outgrowth" of the axon nerve. The pictures that he presented speak entirely for an intraplasmatic extension of the axon nerve.

Foerster's and Goldstein's papers do not seem to me necessarily to contradict each other. In my opinion, there is only a difference in the method of consideration of the same problem. When a patient with a serratus paralysis is requested to raise his arm, he can do it only incompletely, and he sets into motion a number of assisting mechanisms in order to attain a possible complete execution. From the standpoint of "totality function," it is an attempt at adjustment of the defect, even though incomplete, similar to that in Goldstein's case of hemianopia. There seems to be no good reason in this disturbance of the "totality function" to look for a circumscribed morphologic pathology, corresponding to the localization theory. None the less, the fact remains that the disturbance of the whole can be assigned to a sharply limited loss of function, namely, the serratus paralysis, which permits an exact central localization.

DR. J. BOEKE: I have never denied that the nerve fibers can grow out freely. I called attention in my paper to the experiments by Harrison and Cajal.

But it is to be remembered, in cutting through the nerve, that surrounding cells are also cut and injured, and it cannot be said that the axis cylinder passes through this living tissue and then again grows out freely. When the gold after-stain is well done, one is always surprised to find the protoplasmic covering everywhere. It must be remembered that the neurofibril strands, together with their "club-shaped growth," in life are apparently diffused in number and certainly possess no such power as the strong fibrils may develop, forcing their way through the tissue elements. Whether the conducting cells are all of ectodermal nature or whether they may also be mesodermal is difficult to decide. But the development of the peripheral nerve systems, in which the motor nerves form their endings in mesodermal muscle fibers, the definite manifestations of regeneration and Grigorieff's experiments on cultivations in vitro which showed nerve fibers growing in mesodermal myoblasts indicate that a close connection between nerve endings and connective tissue elements of a mesodermal nature is possible. To answer Minkowski, it is to be said that by the term "harmony" is understood only that in regeneration not only the nerve fibers but also a collective activity of all the different tissues take place, in which all tissue elements in a harmonious way show changes.

DR. H. SPATZ: In answer to Pfeifer, that blood vessels are present in the cicatricial tissue of a punctured wound does not in the least speak against its glial character; in Alzheimer's lesions, blood vessels are regularly to be found (the condition is therefore also spoken of as "perivascular gliosis"). The granular cells of the earlier stage may as well be of mesodermal as of ectodermal origin. In later stages, on the other hand, there are present protoplasmatic glia that have not yet formed glia fibers. Further investigations along Pfeifer's line are most desirable. My assumption that the new formation of the central nerve fibers here has taken place in glial tissue will agree with most other experiences. The opinion of Bielschowsky that the newly formed fibers enter the vascular sheaths is not shared by others. Answering von Mayendorf, the appearance of myelinated nerve fibers in atrophic lesions in granular cortical atrophy depends on three factors: (1) the size of the lesion (the fibers are more numerous in smaller ones); (2) the duration of the lesion (in the early stages the fibers are nearly always missed), and (3) the age of the subject (in younger persons they are very abundant, and in older persons more scanty; in very old persons they may be missed entirely). Again, the glia cicatrices, even in the myelin picture, appear empty. That the "myelin spots" that I have presented are accumulations of myelinated fibers is outside any question. It must be assumed that the newly formed fibers are the outgrowths of fiber stumps from the borders of the lesion.

DR. R. MATTHAEI: Regarding Minkowski's statement, I may say "totality," entireness, is not merely a word that fits in where we lack knowledge. If I understand Minkowski correctly he expressed a fear that the conception of "totality" is not sufficiently proved. Essential for its understanding is the following point of view: It is not necessary to believe; one can conceive totality of the organism through the description of many parts and from this reconstruct totality. Totality is something superordinated, in contrast to the new parts, the qualities of which I do not even wish to characterize. The conception of objective striving is connected with the whole. To repeat, objective striving depends on the recognition of the characteristics of the organism. But it is not necessary to stop with this conception. Much more does it depend on the description of the (functional) structure of the activities of objective striving. One must attempt to discover its laws. Also the conception of harmony is to be understood in relation to the entire organism. A contrary relation would be present if the organism to a certain extent were accidentally composed of independent individual mechanisms. It is not possible to injure a part of the organism without at the same time influencing the rest, and bringing about a change in the whole. From this standpoint harmony embraces totality.

DR. O. FOERSTER: Weiszäcker declared that there is an insurmountable gap between Goldstein's conception and mine, since Goldstein denies the substitution of one part of the nervous system for another, while I admit it to be so. That I cannot assume that the function of the optic nerve can be replaced by the auditory nerve is unnecessary for me to state. But when several organs serve a common function, forming a collective working group, and one member becomes incapable of function, and then after a beginning of functional ability of the collective group the function again is restored either completely or partially, I fail to see why it cannot be said that the remaining members have undertaken the function of the one that has fallen out. This is clear and understandable. Weiszäcker thinks that no statement can be made regarding the function of individual parts of the nervous system. When it is established that in stimulating a peripheral nerve a contraction develops in the muscles that it supplies, and when after sectioning this nerve the muscles can no longer be made to contract, I fail to see why it is not justifiable to say that it is the function of the peripheral nerves to innervate the muscles. If one is asked to give up this old terminology as untenable, something else must be put in its place, something that can be understood and discussed. Regarding chronaxia, I called attention several times to the fact that it offers the finest method for measuring sensory disturbance and that similarly it is useful in determining restoration of sensibility. Finally, Weiszäcker declared that my paper failed to show scientific proof that an objective striving must be assumed. I did not lay claim to such proof. I distinctly stated that in my desire to explain restitution processes everywhere at a definite point there was no proceeding further, and that I could not explain to myself the processes without assuming a principle of suitability for the need. This is entirely a personal opinion. Minkowski was of the opinion that proof was not presented that the homolateral pyramidal tract partakes in compensation. I have expressly said that I considered the hypertrophy of the remaining pyramidal tract nothing other than the morphologic expression of the replacement of this pyramidal tract for the one that was lost. But that the homolateral pyramidal tract is of importance in the restitution of hemiplegia can be seen from the fact that in an extensive restored hemiplegia, when the other pyramidal tract is lost later, the former restored ability for isolated innervations and for modification of stereotyped extrapyramidal synergies is again lost. So far I do not know of any individual corticospinal conducting tract, aside from the pyramidal, that is capable of bringing about individual innervations. I shall not deny the existence of such. But the part played by the homolateral pyramidal tract appears to me to be established by the facts mentioned.

DR. K. GOLDSTEIN: I cannot agree with Foerster that every one knows what is meant by performance and symptoms. Ordinarily they are understood as practical conceptions that one acquired from some manifestations, and when one holds them for the phenomena themselves, one is under the influence of a definite theory. This, for example, is the case with the conception of the nervous system as a composite of reflex apparatus, the performance as reflex performances, and the manifestation in injury of the nervous system as a loss of some of the functions. It appears to me to be one of the most important and difficult problems, when one desires to understand the essence of restitution; to explain conceptions such as performance, function and symptoms is difficult since it is possible to do so only through a comprehension of the organism as a whole. To be sure, there are more peripheral functions the disturbance of which eventually may be corrected. A mechanical correction may here be sufficient. But in most cases the consideration of the defect must be from the point of view of its importance to the entire organism. The followers of the atomic consideration of function must also admit this; they too make use of such conceptions as entirety and purpose. But these conceptions to a certain extent appear then only as expedient, and need a closer determination. If the consideration of the whole is not to remain a mere phrase, the method of investigation that can lead to the conception of the whole must be given clearly, and must be concretely characterized in a given case. The method

of investigation that comes into consideration is the dialectic progressive experience. The whole can never be put together from the parts, since the parts are not true parts of the whole; but through isolated thinking, artificial abstractive developed factors represent the whole, which first receive their designation on consideration of the whole. On the other hand, it must begin with the parts. Through such a consideration one gains a picture of the whole, which only the experience gained from the parts can perfect and enlarge, and through which the conception of the whole is justified. In this way one arrives at a progressive recognition of the "nature" of an organism, indeed of man. Only this recognition, in which the highest possible conception of usefulness plays no part, creates the basis for all considerations concerning function and its restitution. Thus every rational therapeutic undertaking presupposes a difficult analysis of the interpretation of the symptoms. This requires new conceptions and new terms; it is not merely a question of a different conception of the same facts; in similar facts there can be but one conception, at any rate but one that is right. As a matter of fact, it is also concerned with different facts, corresponding to the different ways of consideration. What the newer considerations uncover in reality is something different. The old view operates too exclusively with a characterized conception of content; the newer views demand conceptions for the course of the occurrence in the normal organism and the changes in the course in the damaged organism. Characterizations such as "control corresponding to the realization of an organism's function to perform, to the real receivable performance," "control corresponding to an avoidance of dangerous reactions," etc., are not new terms for old things; they are new conceptions, and they are necessary because they make one understand not only what takes place in the organism, especially the occurrences in pathologic changes of the organism, but also the manner of repair. The new conceptions do not do away with the old ones; the latter receive their importance in the consideration of the whole. Thus, as an example, the reflex now appears as a special form taking place under very special conditions, not as the form on which is built everything that takes place, etc.

Book Reviews

Das Genie-Problem. Eine Einführung. By W. Lange. Price, 2.80 marks. Pp. 125. Munich: Ernst Reinhardt, 1931.

The author presents in condensed form an introduction to his larger work on "Genius, Insanity and Fame," which is the outcome of an extensive and intensive study of a large literature and 170 pathographic sketches. It is not merely the unusual talent, but especially the emotional stir caused by the performance and its effects within the spirit of the period that creates the evaluation as genius. The real feature of genius is the extent of recognition elicited. This does not ignore the fact of talent, but the emphasis is put on the fashion and line of sensitiveness of the period. Genius is not a tangible variety of mankind, but a sociological phenomenon. In connection with the important relation to insanity, the book offers a glossary of psychiatric terms. Most geniuses were never psychotic but largely psychopathic. The performance and fame and social response have to be studied independently to get the correct picture. The last chapter is devoted to the relation of the genius to culture. Lange groups the types as: (1) healthy, highly talented (Raffael, Titian, and others — Leibniz), mostly too generally intelligible to be evaluated as geniuses; (2) healthy and successful, but without especially high talent — as Columbus; (3) psychopaths with high talent (Michelangelo, Luther, Beethoven, Nietzsche, Strindberg); (4) psychotics or psychopaths with moderate talents, but evaluated as saints, etc. (Mohammed, Swedenborg and others); (5) healthy, talented leaders, artists and poets (Horace, Virgil, Freytag and Sudermann); (6) "success" persons without necessarily great talent, but "stars," etc.; (7) persons who went through phases, marking them as Goethe was marked during the Werther period, Napoleon as general. The remaining five groups are geniuses through oddity, but always because of a special responsiveness of the times.

The idea of genius as largely a social phenomenon and function is certainly provocative. It would seem to explain more why one speaks of "genius" than what kind of person the genius is. A somewhat pessimistic trend makes the author end with: "Man is a tragic animal . . . . in discord to the very bottom of his being, in discord as a matter of fact anyhow." For a proper evaluation of the point of view and the mass of material covered, it is no doubt necessary to allow oneself to enter into the spirit of the larger book as well as this smaller introduction; otherwise, one might easily be influenced too strongly by the numerous casual, but usually stimulating side-glimpses.

Studien zur Psychologie und Symptomatologie der progressiven Paralyse. By Paul Schilder. Price, 15 marks. Pp. 176. Berlin: S. Karger, 1930.

This monograph represents a further step in the author's attempts at the understanding of the psychologic mechanisms at work in organic mental diseases. Although the studies reported here have been undertaken in cases of dementia paralytica, the discussion includes a number of allied manifestations, such as the other dementias, Korsakoff syndromes, organic deliria, etc. The point of view taken is that, no matter what the cause of the abnormal mental state may be, the psychic manifestations always preserve a definite dynamic relationship to the central personality structure. The monograph opens with a brief presentation of the author's well known theory of the structure and functions of the human mind with special reference to the mechanisms of language, thought processes and memory. This is followed by a report of the special studies undertaken in these cases. For this purpose a large and representative number of cases of dementia paralytica were subjected to a uniform clinicopsychologic study. The usual

bedside observation of the behavior, mood, emotional states and intellectual deviations of the patient was supplemented by special investigations of the retention memory on the basis of the reproduction by the patients of stories told to them. In these, special attention was paid to the distortion of the content, consisting in the dropping of some of the details, the addition of new ones or the change of some contained in the story.

In analyzing the results of the studies, the author shows clearly that the distorted and apparently unintelligible productions of the patients become psychologically understandable when they are approached from a dynamic point of view. The reproductions of the stories, as well as the delusions and misinterpretations, met with in this disease are definitely related to the personality of the individual patient, and the content as well as the form assumed follows lines characteristic to this process.

The comparatively short monograph contains a wealth of ideas, material and suggestions for further lines of attack. True to his style, the author occasionally sacrifices clarity of expression for the sake of increasing the richness of the content. To abstract fully the contents of this extremely valuable contribution it would be necessary almost to write another monograph; a proper appreciation of the study can be gained only from the original.

Sur l'activité spontanée normale et pathologique. By Dr. Abraham Barnett. Pp. 70. Paris: Librairie le François, 1931.

In a pamphlet of seventy pages the author puts together the literature and results of a study of the very important and interesting problem of the total activity of the entire animal and of the entire man, the maintenance of psychobiologic behavior and the activity necessary to escape ennui and to establish a sense of comfortable self-feeling, self-justification, mastery of difficulties, etc. He reports the American work of Richter and Wang of the Phipps Clinic and others, showing the rôle of the motility of the empty stomach as a starter and regulator of the total activity, the effect of various endocrine glands and of the ingestion of phosphates, etc., and the grouping of the observations in psychopathic states and the possibility of regulating the overactivities (mania), the underactivities (depressions) and the dysactivities (simple or schizoid or paranoic). Utilizing the experimental data, he tries to regulate the hunger contractions of the stomach with food, papaverine, benzyl benzoate and sympatheticotonic medications, and reduction of the gonadal activity by radiation or ablation, and in depressions, by vagotonic medications, phosphates, spacing of feedings and injections of extracts containing female sex hormone in men as well as women. Psychoanalysis and psychotherapy are considered in dysactivity.

There is no doubt that man as naturally a motor being deserves this attention. The presentation is stimulating, and the possibly somewhat hasty direct application of the laboratory observations to practical uses is refreshing, although perhaps these observations are less readily applicable than is conveyed in the essentially suggestive review.

Order of Birth, Parent-Age, and Intelligence. By L. L. Thurstone and R. L. Jenkins. Price, $3. Pp. 135. Chicago: University of Chicago Press, 1931.

This is the third of a series of monographs from the Institute of Juvenile Research of Chicago. The first two monographs on "Brain Mechanisms and Intelligence" by Karl S. Lashley and "Delinquency Areas" by Clifford R. Shaw have already been reviewed. This investigation is based on data collected by the Institute. The book is divided into two parts: an analysis of the data taken from the Institute for Juvenile Research and a summary of the literature on this and closely related problems, for which Dr. Jenkins is chiefly responsible. The first part of the study is the work of both authors.

The conclusions are as follows: There appears to be a definite tendency for the intelligence quotient to increase progressively within families, from the first

to the later born members. The first-born are apparently more frequently problem children than their brothers and sisters. The sex of the next older or next younger child apparently influences the behavior adjustment of children. There seems to be a tendency for children of parents widely different in age to be mentally inferior to those of parents more nearly the same age. There is also a tendency for children born six or more years after their next older sibling to be mentally inferior to those in whose cases such a long time has not elapsed between births.

A review of the experimental literature reveals: The optimum position for a normal parturition is, in general, the third to the fifth pregnancy. Length and weight at birth and plural births increase progressively with birth number. There is good evidence that the first-born are very much more frequently subject to congenital pyloric stenosis than the later born children. The first-born are more frequently institutionalized for tuberculosis, and more frequently become criminals.

No further word as to the quality of the work is necessary. The results not only are interesting and instructive, but show the value of carefully obtained histories.

Die Neurosen des Lebenskampfes. By Walter Cimbal. Price, 12.50 marks. Pp. 356. Berlin: Urban & Schwarzenberg, 1931.

In this book of 356 pages, Cimbal discusses in a most thorough and sympathetic fashion the life problems that confront man. He employs the word "Lebenskampfes" in discussing the numerous situations that may arise in the life's battles of an individual. In the opening chapters, Cimbal takes up in an orderly manner the problems that confront the child and carries this study through various stages of the home, occupation, education, social life and spiritual and sexual life. To understand these life's problems it is important to have a thorough insight into normal human psychology. He believes that many of the later psychologic problems of life that are so commonly looked on as inherited or of constitutional character are in reality due to faulty psychobiologic patterns resulting from early experience and improper guidance. It is important that the physician serve as a guide for these persons in arriving at a satisfactory solution for their life's battles.

Cimbal follows rather closely the teachings of Freud and Jung, but he continually reverts to the function of the central nervous system, the sympathetic system and to the influence of the endocrine glands on normal functioning. He believes that complexes and intelligence do not go hand in hand, but are the result of early life patterns. Considerable space is devoted to a discussion of the sexual life of man and woman, and while he treats this in a most realistic manner, he does not fail to give very able therapeutic suggestions.

In the closing chapters Cimbal discusses the differentiation between the psychogenic and psychopathic diseases. One may wonder if here he does not go into too great detail on some minor points, such as toxic disturbances, and then devote only a few pages to such an important subject as the traumatic neuroses.

All in all the book represents a tremendous amount of careful observation and very readily indicates Cimbal's profound interest in his study of life's battles ("Lebenskampfes"). A most excellent bibliography of about 400 references is appended.

Ophthalmo- und Oto-Neurologie. Ein Lehrbuch für Studierende und Aerzte. By Dr. E. A. Spiegel and Dr. Ignaz Sommer. Price, 28 marks. Pp. 366. Berlin: Julius Springer, 1931.

This is a very timely book, for while there appeared recently under the editorship of Alexander, Marburg and Brunner a series of volumes on the neurology of the ear and some years previously a similar work on the eye and the nervous system, these volumes were entirely too large for the average student

and physician. In the present volume chief emphasis is laid on the neurology of the eye and the ear, and in addition there is a discussion of the neurology of the nose, mouth, larynx and pharynx. There are also interesting chapters on the relation of pain to the fifth nerve, complications of the seventh nerve and diseases of the vegetative fibers of the middle ear.

The book begins with a presentation of the anatomy and symptomatology of lesions of the brain stem and brain. This is adequately and well presented. It is followed by a discussion of the cerebrospinal fluid and chapters on the optic tract and symptomatology; the ophthalmoscopic picture in diseases of the nervous system and the ear; ocular movements and their disturbances; involuntary muscles of the eye and orbit, their reactions and pathology; the sensory supply of the ear and its disturbances; hearing and its functional determination and disturbances, and the labyrinth and its function and diseases.

The subject matter is presented with sufficient detail and so logically that there is no question in the reader's mind as to the anatomy, physiology and symptomatology and the results of disease processes. A sufficient number of references are given so that the reader may have the advantage of further investigation. The illustrations are excellent; some are in colors. Diagrams are used to illustrate better the findings, and these are very helpful, particularly in the functional disturbances of the ear and the result of vestibular tests. Altogether it is a praiseworthy book.

Recent Advances in the Study of the Psychoneuroses. By Millais Culpin, M.D. (Lond.), F.R.C.S. (Eng.). Price, $3.50. Pp. 348. Philadelphia: P. Blakiston's Son & Company, 1931.

The author's point of view can perhaps be best presented by a quotation from the preface: "the author has been forced to the conclusion that, apart from modern diagnostic advantages, especially those derived from our knowledge of the central nervous system, and some brilliant descriptive work by the French school, the chief advances in our knowledge of the psychoneuroses since the time of Galen have been the direct or indirect result of psychoanalytical discoveries. This does not mean that the study of the psychoneuroses begins and ends with the analysis of patients, and that this book is only another exposition of psychoanalysis. The interest and importance of recent advances in this subject lie in our changing attitude towards it, and our recognition of its clinical significance. These aspects are dealt with in this volume, so that the reader will know what stage the subject has reached and what are now its relations to general medicine. Only sufficient reference is made to psychoanalytical principles and practice to make the general theme intelligible; for accounts of their latest developments the reader must refer to the fountain head. Since the views of Jung and Adler are by some psychotherapists given more importance than I admit, independent chapters on those subjects have been contributed by Dr. James Young and Dr. A. R. Redfern. Child Psychopathology and the management of a clinic are also treated separately by Dr. E. Miller and Dr. J. R. Rees."

It is altogether a very readable book in which the subject is precisely and concisely presented without the use of too many words. In that regard it is an improvement over some of the more wordy books on similar topics that have come out within the last year. It is of interest that in the chapter on occupational neuroses, in which the subject of writer's and similar cramps is discussed, miners' nystagmus is included.

How to Be Happy Though Human. W. Beran Wolfe, M.D. Price, $3.50. Pp. 377. New York: Farrar and Rinehart, 1931.

In the last year or two the number of semiscientific, or what could be better termed pseudoscientific, books that have been written for the public is appalling. In each the author deplores the volume of such literature and then proceeds to

write another book. For example, Wolfe states in the preface: "A veritable Niagara of pseudo-psychological literature has been poured upon the lay ear," and then dilates on the need of a good book, written by a competent person, and that to meet this need he has essayed the task of writing "a Baedeker of the soul."

The titles of such books are intriguing; "How to Be Happy Though Human," "Love in the Machine Age," "The Academy for Souls," "Machine Made Man," etc., are a few. On the folder there is a diagram illustrating the relationship of society, work and sex to prostitution, perversion, homosexuality, slave drivers and so on. It would seem from all this that much ingenuity has been expended by the authors in seeking attractive titles for their literary wares. The diagrams are much like those used in detective stories to outline the locale of the murder, and yet all this is written in the name of mental hygiene and to aid the defenseless public. How long will this continue?

The Selected Writings of John Hughlings Jackson. Volume 1. On Epilepsy and Epileptiform Convulsions. Edited by James Taylor, with the Assistance of Gordon Holmes and F. M. R. Walshe. Price, 25 shillings. Pp. 500. London: Hodder and Stoughton, 1931.

American neurologists have always paid tribute to the works of John Hughlings Jackson; therefore, the appearance of the first volume of selected writings is more than welcome. Dr. Taylor, the editor of these volumes, in 1925 collected and republished under the heading of "Neurological Fragments" some of Jackson's shorter notes. Dr. Taylor's introduction to this volume is praiseworthy, and all neurologists are indebted to him for the care that he has taken in collecting and editing these papers.

It is difficult not to moralize on the quality of Jackson's work in comparison with the present. Most original articles of today are far removed from the philosophical writings of Jackson. Many of them are experimental or neuropathologic. Clinical investigation occupies little space in neurologic publications of today. Philosophical writing is a rarity, and yet we need philosophy just as much today as in the time of Hughlings Jackson. This is not to say that there have not been great advances in neurology, for there have; in fact, neurology has never been in a healthier state than it is now, but there are not enough of the sort of contributions that made Jackson great.

Although Jackson was not interested specifically in psychiatry, nevertheless, his writings show deep insight into psychology. His views on aphasia are the views of today, and he anticipated the present conception of this subject. It would be well for the future of psychiatry if there should be a modern Jackson who could develop a psychiatric philosophy that would endure. There has never been a time in the history of psychiatry when this has been more needed.

Conditions and Consequences of Human Variability. By Raymond Dodge, Professor of Psychology, Yale University. Price, $2.50. Pp. 162. New Haven, Conn.: Yale University Press, 1931.

Professor Dodge is convinced that a study of human variability not only is as important as a study of hypothetic constancy, but also brings us closer to the facts of mental life as an important condition of its development, and opens the way to an understanding of its nature. This is a very interesting concept, and the author discusses his thesis from the laboratory and clinical standpoints, always assuming an anatomic substratum for his conceptions.

After an introduction, he discusses the influence of the refractory phase on behavior and quotes some of his own work on the knee jerk and lid reflex. This is followed by chapters on the influence of relative fatigue; inhibition and variability; inhibition and summation, in which the views of Pavlov, Fröhlich, Keith Lucas, Adrian and Forbes are discussed; also by a discussion of the effects of faint stimuli on human sensory and motor reaction systems, in which the author

again quotes some of his work on lid reflex response to sound stimuli, and in the field of visual perception of chroma, and an interesting chapter on the occasional development of behavior in simple patterns. In an interesting discussion on the interaction of neural strata, the author states his belief that many, if not all, adaptive acts of adult man are really complicated responses determined at several levels of integration. He believes that they commonly begin as a relatively crude approximate adjustment of short latency, which may be called protoprathic, and develop into more adequate adjustments, which may be epicritic.

Perhaps the most interesting chapters are on the subject of cortical systematization and the consequences of persistent cortical systematization, and the last two chapters on the relationship between mind and brain and mind without brain.

Altogether this is a stimulating work and points the way to scientific investigation in the realm of psychology and neurology.

Institute for Child Guidance Studies. Selected Reprints. Edited by Lawson G Lowrey, M.D. Price, $1.50. Pp. 290. New York: Commonwealth Fund, 1931.

Before establishing the Institute for Child Guidance in 1927, the Commonwealth Fund organized and conducted experimental clinics for child guidance in various cities throughout the United States. The New York Institute for Child Guidance is in a way the principal of these institutes, for it is supported directly by the Commonwealth Fund and is more of an experimental and complete institute than any of the others.

The publication here reviewed is the first volume containing reprints of publications by members of its staff. The contents have been divided under several headings: contributions in the social field, medical field, psychological field and, lastly, child training, comprising altogether sixteen articles.

It would be difficult to review the contents of these articles. Suffice it to say that it represents an excellent cross-cut of the literature on child guidance. In the realm of psychiatry, particularly of child psychiatry, child guidance studies have formed distinct advances in the welfare of children, and the Commonwealth Fund is deserving of high praise for its broad vision, philosophical conception and the thoroughness with which it has embarked on and carried out this well merited work.

Handbuch der Geisteskrankheiten. By Oswald Bumke. Volume 8. Price, 76 marks. Pp. 728. Berlin: Julius Springer, 1930.

This eighth volume of Bumke's Handbuch deals with the etiology and pathogenesis of dementia paralytica and the nonparalytic psychoses, by A. Hauptmann; the syphilitic psychoses and the clinical aspects of dementia paralytica by Bostroem, and the treatment for the syphilitic psychoses by Plaut and Kihn. F. Stern presents the arteriosclerotic psychoses, Runge the mental disorders of the female and male climacteric and involution period, and the psychoses of senility (including also Alzheimer's and Pick's disease). The epileptic reactions and epileptic diseases by Gruhle close the volume. The presentation and bibliography are in keeping with the standards of this comprehensive survey of the field, as may well be expected of the authors long known as leading investigators of these fields.

The Medical Department of the United States Army in the World War. Volume X. Neuropsychiatry. Prepared under the Direction of Maj. Gen. M. W. Ireland, Surgeon General. Price, $2.25. Pp. 543. Washington, D. C.: U. S. Government Printing Office, 1929.

Volume 10, on neuropsychiatry, of the series issued by the Medical Department of the United States Army in the World War, is of particular interest to neuropsychiatrists, for it deals with such activity in the United States and in the American Expeditionary Forces. It begins with a preface by Col. Thomas W.

Salmon, the chief medical officer in the A. E. F. The contents are then divided into two sections, the first dealing with medical history in the United States, the second in France.

It is difficult to review a book of this kind. It is full of information of the manner in which the department was organized, its personnel, the provisions for the care of patients with mental and nervous disorders, their treatment and their disposition. There are besides special chapters on the treatment of certain selected groups, such as the War Neuroses Hospital, including a postwar study of a typical group of cases of war neuroses in 1919 to 1920, and 1924 to 1925.

Altogether it is a stimulating book, for the Neuropsychiatric Corps of the United States Army did its job well.

Les syndromes cérébelleux mixtes. By A. de Almeida Prado. Price, 30 francs. Pp. 168. Paris: Masson & Cie, 1931.

Literature from South America is not common; therefore, the work of Professor Prado, from the Faculty of Medicine of São Paulo, Brazil, is welcome. The author has classified mixed cerebellar syndromes. The translation has been well done by Dr. M. Nathan. He has divided the subject into the syndrome of the superior cerebellar peduncles, the middle cerebellar peduncles, the inferior cerebellar peduncles and the syndrome of compression of the cerebellar hemispheres, and in the last chapter he discusses four maladies that give cerebellar symptomatology, that is, dementia paralytica, disseminated sclerosis, epidemic encephalitis and Friedreich's ataxia. The author records a number of his own observations.

While there is nothing new in the book, the subject is well summarized and serves a distinct purpose. It is a pity, however, that the French literature, with rare exceptions, is alone consulted. The English and American literature, especially on the cerebellum, is quite large and merits consultation.

Handbuch der biologischen Arbeitsmethoden. Abteilung V. Methoden zum Studium der Funktionen der einzelnen Organe des tierischen Organismus. Teil 5 B, Heft 6. Methoden zur Erforschung der Funktionen des Kleinhirns. By J. ten Cate, Amsterdam. Price, 5.50 marks. Pp. 95. Berlin: Urban & Schwarzenberg, 1931.

The author has done a service to cerebellar knowledge in gathering together the results of the different methods of investigation of the functions of this organ. He has contributed somewhat himself to such knowledge. The subject matter is well presented in about 100 pages. His conclusion is that the function of the cerebellum is by no means definitely known and that more definite knowledge is still to be sought.

In spite of contributions to cerebellar physiology in the references at the end of the book, only few American authors are mentioned. This is inexcusable, for the contributions of Riley, Mussen, Pollock and Davis, among others, are available in the present-day literature. Such omissions as these lead to a doubt of the value of the whole.

Brain and Spinal Cord. A Manual for the Study of the Morphology and Fibre-Tracts of the Central Nervous System. By Emil Villiger. Edited by William H. F. Addison, B.A., M.D. Fourth edition. Price, $6. Pp. 337. Philadelphia: J. B. Lippincott Company, 1931.

This work on the anatomy of the nervous system needs no introduction to American neuropsychiatrists. Since its first publication it has been successively revised, and this edition as well as the last has been undertaken by Professor Addison. Very few changes have been made in the present volume. The changes consist in a description of the present-day conception of the neuroglia, and several new drawings simplifying the connections of the extrapyramidal system; three

new drawings have been inserted to show the fiber tract preparations in the cerebral hemisphere. The changes in the text are principally in connection with the new or altered figures. This book is undoubtedly the best manual for the study of morphology and the fiber tracts of the central nervous system.

A Text-Book of Neuro-Anatomy. By Albert Kuntz, Ph.D., M.D. Price, $5.50. Pp. 359. Philadelphia: Lea & Febiger, 1931.

This book of 359 pages is divided into 22 chapters and begins with the origin and differentiation of the neural tube; then follow the topography of the central nervous system, cerebrospinal pathway, the morphology of the nerve cells, interstitial tissue of the central nervous system, nervous integration and then in logical order the internal structure of the whole nervous apparatus. The discussion of the autonomic nervous system is based on chapters 1 to 5 of the author's book on this subject.

The anatomic discussion is adequate, but the physiology and especially the clinical symptomatology leave a great deal to be desired. Too many things are taken for granted. The illustrations are well selected.

La myotonie atrophique; (maladie de Steinert); Sa place entre la maladie de Thomsen et les myopathies. By Dr. Lucien Rouquès. Price, 32 francs. Pp. 229. Paris: Amédée LeGrand, 1931.

This monograph, coming from the clinic of Guillain at the Salpêtrière, Paris, is an excellent review of the problems of various myopathies. The book is divided into eighteen chapters, which take up all the problems, symptomatology, causes and treatments of myotonia atrophica. The author concludes from his analysis that the disease is probably due to some disorder of that part of the central nervous system that exerts a trophic influence on end-organs. He believes that the endocrine and muscular manifestations of the disease have a common origin. The book is illustrated and has an excellent bibliography. It is to be recommended to those interested in the problems that the various types of muscular dystrophy present.

News and Comment

POST-GRADUATE COURSE IN NEUROLOGY AND PSYCHIATRY, VIENNA, 1932

The next intensive post-graduate course in neurology and psychiatry will be held in Vienna, Austria, from June 27 to July 31, 1932, inclusive. Applications should be sent to the American Medical Association of Vienna, where further information can be obtained.